VOLUME 97 • MAY 1959 • NUMBER 5

A.M.A. JOURNAL OF

DISEASES OF CHILDREN

PART I

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Mary Ellen Avery and Jere Mead

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Arturo J. Aballí, Valeriano López Banús, Sergio de Lamerens, and Simón Rozengvaig

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IV. Deficiency of Stuart-Prower Factor as a Part of the Clotting Defect of the Newborn

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Multiple Metaphyseal Fibrous Defects
William A. De Young and Edwin M. Wright

Abstracts from Current Literature

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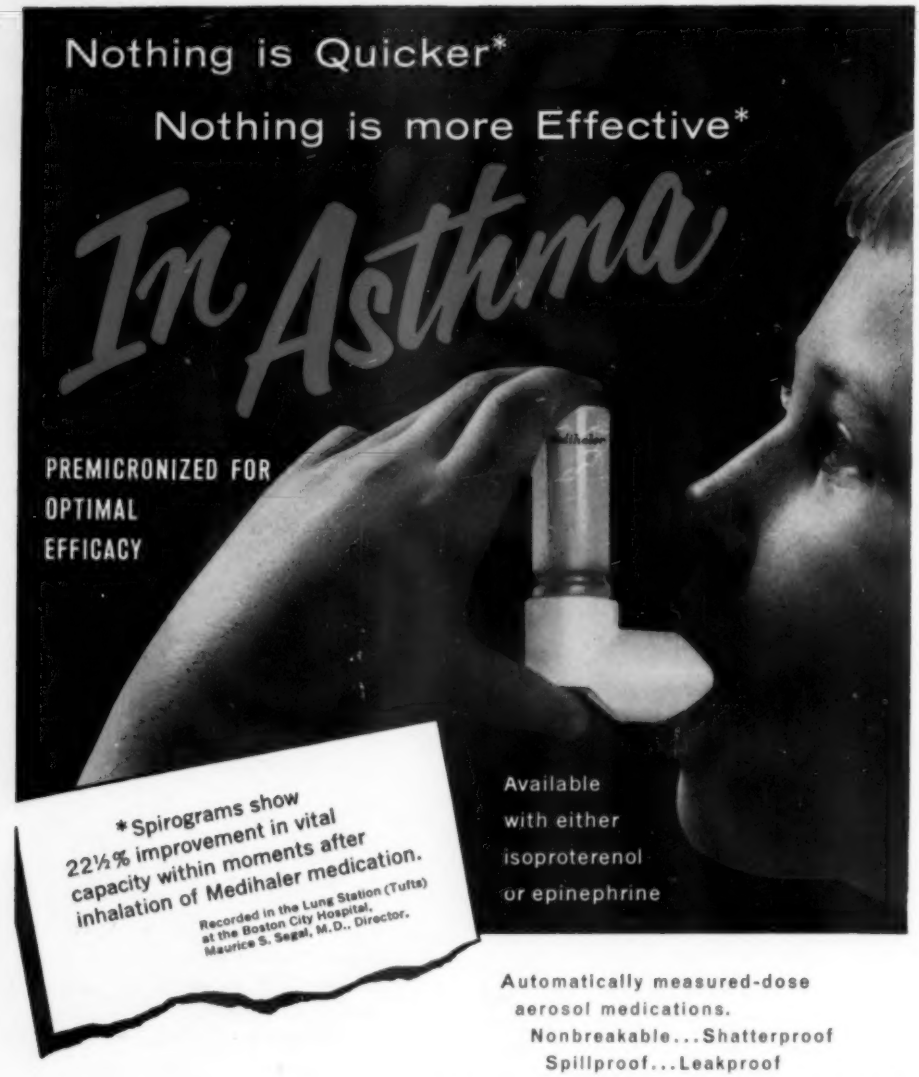
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TABLE OF CONTENTS

VOLUME 97 MAY 1959 NUMBER 5

PART I

ORIGINAL ARTICLES

PAGE

Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease
Mary Ellen Avery, M.D., and Jere Mead, M.D., Boston 517

Coagulation Studies in the Newborn Period
Arturo J. Aballi, M.D.; Valeriano López Banús, M.D.; Sergio de Lamerens, M.D., and Simón Rozengvaig, M.D., Havana, Cuba
III. Hemorrhagic Disease of the Newborn 524
IV. Deficiency of Stuart-Prower Factor as a Part of the Clotting Defect of the Newborn 549

Muscular Dystrophy
T. S. Danowski, M.D.; J. Van Diermen, M.D.; A. C. Heineman Jr., M.D., and F. M. Mateer, M.D., Pittsburgh 555

The Effect of Large Doses of Prednisone on Acute Rheumatic Fever
Charlotte Ferencz, M.D., Cincinnati; Milton Markowitz, M.D., and Joseph J. Bunim, M.D., Baltimore 561

Parenteral Trypsin in Trauma
Thomas G. Glass Jr., M.D., Houston, Texas, and Albert Fischer, M.D., San Antonio, Texas 571

Bilateral Dwarfed Kidneys
R. K. Slungaard, M.D., and J. L. Jaeck, M.D., LaCrosse, Wis. 575

The Concentration of Potassium in the Plasma
Hans G. Keitel, M.D., Philadelphia, with the Technical Assistance of Jocelyn Blakely 583

Kernicterus in Rats with an Inherited Deficiency of Glucuronyl Transferase
Lois Johnson, M.D.; Felicitas Sarmiento, M.D.; William A. Blanc, M.D., and Richard Day, M.D., New York 591

An Epidemic of Infectious Hepatitis in the Children's Service of a Psychiatric Hospital
A. J. Noordsij, M.D., Ingleside, Neb. 609

Vaginitis in Children
Margaret Thorne Grossi, M.D., and Myron I. Buchman, M.D., New York 613

CLINICAL NOTES

Successful Treatment of Cardiac Arrest During Exchange Transfusion
G. H. Glassford, M.D., Chicago, and F. F. Motamedy, M.D., Los Angeles 616

Multiple Metaphyseal Fibrous Defects
William A. De Young, M.D., and Edwin M. Wright, M.D., Saginaw, Mich. 617

REGULAR DEPARTMENTS

Abstracts from Current Literature 619
News and Comment 648
Books:
Books Received 649
Book Reviews 653

A. M. A.
Journal of Diseases of Children

VOLUME 97 MAY 1959 NUMBER 5

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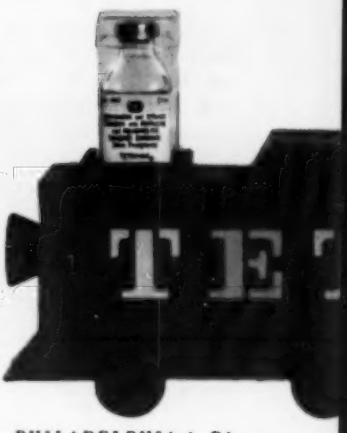

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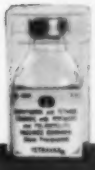

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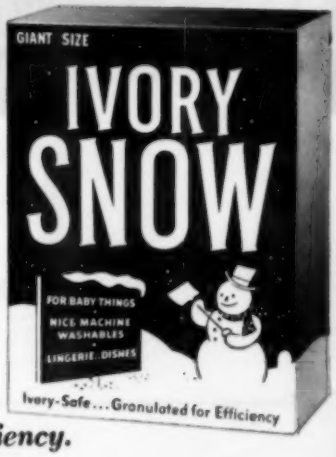

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Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease

MARY ELLEN AVERY, M.D., and JERE MEAD, M.D., Boston

Recent observations suggest that a low surface tension may be an important attribute of the lining of the air passages of the lung.[1-4] The purpose of this paper is to present evidence that the material responsible for such a low surface tension is absent in the lungs of infants under 1,100-1,200 gm. and in those dying with hyaline membrane disease. The role of this deficiency in the pathogenesis of the disease is considered.

Surface tension operates so as to minimize the area of the surface. In the lungs, where the internal surface (the alveolar lining) is curved concave to the airway, the tendency of the surface to become smaller promotes collapse. Although the forces not only of surface tension but also of the elastic tissue tend to collapse the lungs, their behavior differs in one important respect. When the lung contains only a small volume of air, the elastic recoil of the tissue is diminished, that is, the less the tissues are stretched, the less are the elastic stresses. In contrast, the contribution of surface tension to the retractive force of the lung is increased. Thus, as the air spaces become smaller and more sharply curved, the "mechanical advantage" of surface tension may be thought of as increasing, promoting the tendency to collapse. Since the air spaces are not uniform in size and are all connected to the airway, the smaller, more sharply curved ones tend to empty their contents into the larger. A high surface tension would favor this phenomenon and predispose to atelectasis, whereas a low surface tension would be a stabilizing influence, diminishing the tendency to collapse. For example, if an alveolus can be thought of as a partial sphere with a radius of 40μ and a surface tension equal to that of plasma (55 dynes/cm.), pressure difference would be 20.5 mm. Hg between the inside and outside of the sphere.* This is the pressure tending to collapse the alveolus. If, however, it had the same radius but a surface tension of only 5 dynes/cm., the pressure tending to collapse it would be 1.86 mm. Hg.

Pattle, and more recently Clements and Brown have focused their attention on the magnitude of the surface tension within the lung. Pattle,[1,2] noting the stability of foam and bubbles arising from the lung, concluded that their surface tension must

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From the Department of Physiology, Harvard School of Public Health, and the Newborn Service, Boston Lying-In Hospital. Research Fellow in Pediatrics, Harvard Medical School (Dr. Avery). Associate Professor of Physiology, Harvard School of Public Health (Dr. Mead).

* This is in accord with the LaPlace relationship, $P=2T/r$, where P is the pressure across the wall of the sphere; T is surface tension, and r is the radius of the sphere.

be extremely low. On the basis of measurements which showed that these bubbles were more stable than those produced from plasma or transudates, he deduced that the bubbles from the lung were lined by a material which he thought was derived from the internal surface of the lung. He suggested that absence of this material in the lungs of premature infants might play a role in atelectasis neonatorum and hyaline membrane disease.

Clements [3] and Brown [4] demonstrated that the tension of a surface film derived from the lung was not a constant value; when the surface was stretched the tension was relatively high (40 dynes/cm.), but when the surface area was decreased the tension fell to 10 dynes/cm. These workers first pointed out that such a reduction in surface tension during deflation of the lung would tend to stabilize the air spaces by permitting them to remain open at low lung volumes.

It must be noted that the measurements made by Pattle and Clements and Brown were on material derived from the lung, and not on the alveolar surface itself. Pattle's assumption was that the material lining the internal surface of the lung would also cover small bubbles expressed from its cut surface. Clements and Brown assumed that if a portion of lung were cut in small pieces and stirred with saline, the most surface-active material in the mixture would seek the surface where its tension could be measured. None of these workers knows the precise chemical nature of the surface film studied. However, the observation that the films can be altered by incubation with trypsin and pancreatin suggests that they are at least in part protein.

For the study of the surface behavior of proteins, the classical methods employing a capillary tube or a platinum ring are inadequate since they record only a single value. The surface tension of protein films changes when the area of the surface is changed. Film balances such as the Langmuir-Wilhelmy type used by Clements permit measurements of surface tension as a function of changes in surface area.[5] The dependency of tension on area is an important elastic-like property of protein films. In surface films obtained from lungs the change in tension is not a constant value, but continues to change in time. It is presumed that in addition to elastic behavior there is a time-dependent viscous component, which produces this lag in response, termed hysteresis.[6] Thus the films derived from the lung behave as if they were viscoelastic entities.

Despite the lack of direct measurements of surface tension at the alveolar-air interface, the low values obtained by Pattle and Clements and Brown with indirect methods would account for the stability of an alveolus at end-expiration. If then the prevention of atelectasis depends on the presence of a material with a very low surface tension lining the air spaces, it seemed attractive to examine the lungs of small premature infants and those dying with hyaline membrane disease for this material. In these infants there is always some atelectasis. The absence of a low surface tension in extracts of their lungs would support the theory put forward by Pattle and Clements and Brown, and at the same time explain the predisposition of these infants to atelectasis.

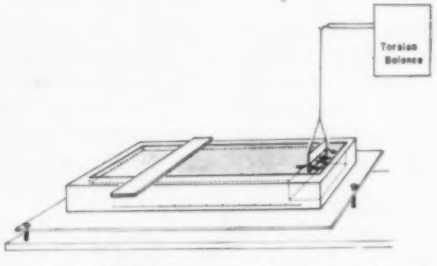


Fig. 1.—The dimensions of the trough are 15×7.5×1.7 cm. outside, 11.8×5×1 cm. inside. At one end is a well 5×1.5×1.3 cm. to permit submersion of the stirrup for a zero reference point. The trough is filled so that barrier touches the surface (65 ml.). A centimeter scale is attached to one side to permit measurement of the area where the barrier is moved. The metal plate under the trough is supported by three screws to permit leveling.

Methods

The method to be described is similar to that used by Clements. The film balance is shown in Figure 1. The trough is constructed of a single block of polytetrafluoroethylene (Teflon).† (This has the advantage over paraffin-coated troughs in that it is less wettable than paraffin, chemically inert, and provides a surface which is easy to clean.) A thin, frosted platinum strip or "stirrup" is partially submerged in the fluid. The force of surface tension, pulling down on the wettable stirrup,‡ is measured on a torsion balance with attached transducer through a direct-writing oscillograph.

Four grams of lung was cut into pieces approximately 2 by 5 mm. and diluted with 65 ml. of 0.85% saline. The mixture was stirred vigorously for about five minutes, filtered through gauze, and poured into the trough. The surface was "aged" one hour before testing. To change the area of the surface, a Teflon strip (11.3 cm. × 2.2 cm. × 0.3 cm.) under a heavy brass bar used as a barrier, was moved once a minute in 1 cm. steps, starting from the end of the trough opposite the stirrup and approaching 0.5 cm. from the stirrup (15% of the original area). The precedure was reversed to extend the film.

A change in surface area was promptly followed by a maximal change in tension, which decreased with time. By the end of one minute at tensions above 20 to 30 dynes per centimeter about 90% of the change has taken place.

At lower tensions the surface appeared irregular and occasionally had whitish linear streaks parallel to the barrier. This easily recognizable change was considered a "gelling" of the film. When this occurred the initial and one-minute readings were nearly the same, and the tension remained constant even on further compression of the surface. Thus there seemed to be a lower limiting tension, often about 5 dynes/cm. At lower tensions when the film did not "gel," the surface tended to creep over the edge of the trough, gradually extending the area so that the one-minute readings had no meaning in terms of tension at a given area. When this happened only the initial value was recorded. (The initial readings at all areas are called dynamic values. The one-minute readings are called quasistatic values.)

The possible influence of concentration of tissue on the results was studied by using 0.5 gm. of lung per 65 ml. of saline and 20 gm. of lung per 65 ml. of saline. The highest and lowest tensions recorded were the same. No attempt was made to establish the minimal amount of tissue needed. Four grams per 65 ml. was the concentration used in these experiments because of convenience in handling this amount.

The possibility that the age of the tissue after death would alter the surface behavior was investigated because the samples of human lungs were obtained at different times post mortem. Therefore samples of dog lung were studied immediately after the animal was killed, and after either refrigeration or freezing for as long as six days. Within these limits there was no significant change in the results obtained.

Temperature changes, within the range of 70 to 101 F and changes in pH of the substrate by addition of HCl and NaOH to a range of pH 1-pH 11 did not influence the surface tension-area relationship. Most of the measurements of the human lungs were made at temperatures between 75 and 85 F, while the pH of the filtered lung extracts was usually 6.5 to 7.0.

Results

The relationship of surface tension to area as measured on the film balance, is shown in Figure 2. Here the path of changing tension with decreasing area is on the left, and the tension with increasing area is on the right side of each plot. The solid lines connect the points obtained immediately after moving the barrier. The inner dotted lines connect the points recorded after one minute at the same area.

These curves differ from the one published by Clements in that they show a steeper slope at the beginning of compres-

† Dupont registered trade-mark.

‡ One correction necessary when using a partially submerged stirrup is for buoyancy. With a very thin platinum strip, this is almost negligible. It can be measured by recording the tension of a known solution with the stirrup at different depths. If subsequent measurements are made at a given depth, the contribution of buoyancy is known.

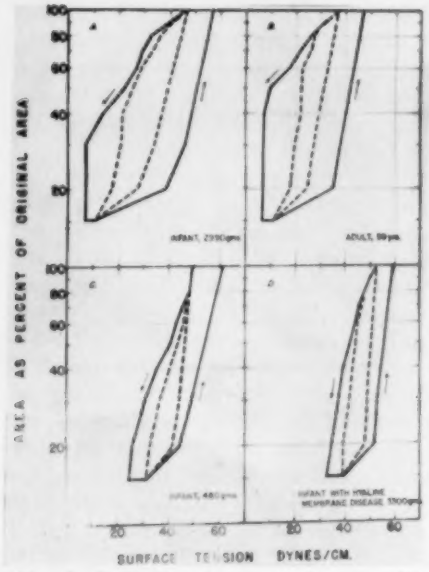


Fig. 2.—Illustrative force-area diagrams. The outer solid line connects the initial values for surface tension obtained when the area was changed. The inner dotted lines connect the values for surface tension after one minute at the given area.

sion of the film. The slope, which is the coefficient of compressibility, is variable, depending on the age of the surface, the number of times cycled and unknown factors. In our experience the least variable values were the lowest and highest tensions recorded. For comparison of the surface behavior of lung extracts from infants of different birth weights, the highest tension reached on extension of the surface, and the lowest tension reached on compression with the means and deviation from the mean are presented in the Table. There is considerable variation in the upper tensions and no pattern is evident. However, a definite pattern appears in the lowest tensions recorded (Fig. 3). The lowest values in the lung extracts of infants under 1,100-1,200 gm. are 20-30 dynes/cm. The lowest tensions in the extracts of heavier infants, older children and adults are under 20 dynes/cm. and usually 5-7 dynes/cm. The only exceptions to this are the lowest tensions measured in the lung extracts of infants dying with hyaline membrane dis-

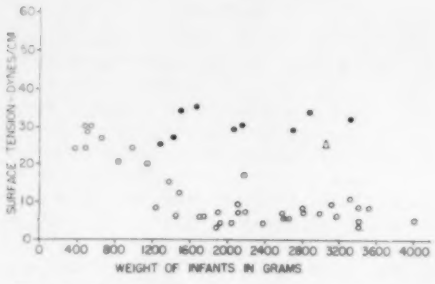
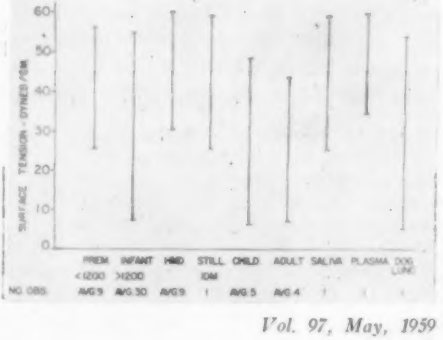


Fig. 3.—Lowest surface tension measured on compression of the surface. Open circles=infants dying from causes other than hyaline membrane disease. Closed circles=infants dying with hyaline membrane disease. Triangle=stillborn infant of a diabetic mother.

ease. In these, the corresponding figures are all above 20 dynes/cm. and most are above 30 dynes/cm. even though the infants were in the weight group where values below 20 dynes/cm. would be expected. This was true in all nine of the infants with hyaline membrane disease studied. The only infant who did not have the disease whose lung had a surface tension higher than expected was a stillborn infant of a diabetic mother.

The behavior of extracts of lungs of dogs, cats, rabbits, and guinea pigs was much the same as that of human lungs. Washings from the tracheal-bronchial tree had the same surface-tension values as lung extracts. However, other tissues, including plasma, whole blood, gastric juice,

Fig. 4.—The horizontal lines connect the highest and lowest tensions measured in extracts of lungs and other tissues. HMD=hyaline membrane disease; still. IDM=stillborn infant of a diabetic mother.



Highest and Lowest Surface Tension of Lung Extracts

Wt., Gm.	Infants Live-born or Stillborn	Highest Tension	Lowest Tension
380	S	49	24.5
470	S	58.2	30.6
480	L	61.5	24.5
500	S	57.5	29
520	L	61	30.5
680	L	56	27
830	L	55	20.8
970	L	59	24.5
1,150	S	49	29
		m=56.2	m=25.7
		± 4.34	± 3.65
1,220	L	52.5	8.6
1,360	L	48	15.2
1,430	L	54	6.6
1,460	L	56	12.2
1,700	L	55	6.1
1,740	L	54	6.1
1,870	L	60	3.6
1,900	S	59	7.3
1,940	S	56	4.9
2,100	S	51.5	9.8
2,125	L	56	7.3
2,180	S	56	17.1
2,180	S	58	7.6
2,390	L	55.5	4.4
2,495	L	61.5	6.8
2,500	L	53	6.1
2,640	L	58	6.1
2,670	L	53.5	6.1
2,800	L	61	8.5
2,800	S	51	7.4
2,900	S	58.2	7.3
3,100	S	61.3	9.8
3,170	S	47	6.1
3,300	S	39.2	11
3,400	L	51	4.9
3,400	L	57.5	8.6
3,400	L	60	3.5
3,515	L	57.5	8.6
4,000	L	52.5	5.4
		m=55	m= 7.6
		± 4.67	± 3.05

	Hyaline Membrane Disease	
Wt., Gm.	Highest Tension	Lowest Tension
1,200	56.5	25.7
1,420	61	27
1,500	60	34.4
1,650	63.5	35.5
2,050	59	29.4
2,150	58	30.5
2,700	62.3	29.5
2,860	59	34.4
3,300	59	32.3
	m=60	m=30.4
	± 1.41	± 3.12

	Children	
Age	Highest Tension	Lowest Tension
9 wk.	54	6.1
3 mo.	51	5.4
8 mo.	51.4	4.9
23 mo.	55.5	7.4
4 yr.	50.6	9.8
	m=46.5	m= 6.7
	± 7.4	± 1.96

	Adults	
Age, Yr.	Highest Tension	Lowest Tension
37	40	9.3
44	41.5	5.4
56	47	7.3
59	46.5	6.8
	m=43.8	m= 7.2
	± 3.53	± 1.61

saliva, synovial fluid, liver, and muscle had surface properties very different from normal lung (Fig. 4).

Comment

The results show that without exception the surface behavior of lung extracts of the nine infants with hyaline membrane disease was different from that of infants dying from other causes and the same as that of infants smaller than 1,200 gm. This suggests that the disease is associated with the absence or delayed appearance of some substance which in the normal subject renders the internal surface capable of attaining a low surface tension when lung volume is decreased.

It is of interest to attempt to relate the results obtained to the pathogenesis of the disease. In all lungs with the first breath, large pressures are necessary to create an air-liquid interface (Table). In this respect the normal lung would not differ from the lung without the surface-active material since surface tension on extension of the surface is similar in both cases. Thereafter, during expiration, the alveolar surface of the normal lung would have diminished tension (Fig. 2), thus reducing the tendency of the air spaces to collapse. On the other

hand, in a lung lacking this lining material, surface tension would tend to remain high during expiration; the air spaces would be unstable, and some would collapse. Once a sufficient number had closed, others would remain open inasmuch as the interpleural pressure at end-expiration would be sufficiently negative to prevent further closure. The net mechanical effect would be a lower than normal interpleural pressure, both at end-expiration and, more particularly, at end-inspiration. This is in accord with the measurements of Cook et al. on living infants with the disease in whom the interpleural pressure at end-inspiration can be calculated to be at least -15 cm. H_2O, about a threefold increase over normal.[7]

As a result of an increased mean pressure difference between the thorax and the rest of the body, intrathoracic blood volume would be increased. In atelectatic regions, and for that matter in air-containing regions as well, presumably the pulmonary capillaries would be influenced by the more negative interpleural pressure and would therefore share in the congestion. The evidence presented by Gitlin and Craig[8] that the membranes contain fibrin, derived from the pulmonary circulation as fibrinogen, indicates that transudation occurs in hyaline membrane disease. There is no evidence that the congestion resulting from the increased body to thorax pressure difference would be sufficient to account for this transudation. It is possible that surface forces may produce highly localized distention and leakage of capillaries, although it is probably true that Pattle's estimate of these effects is an oversimplification.[1]

It is of interest that atelectasis, of the type seen in hyaline membrane disease, but without any membrane, has been described.[9,10] Potter suggests that it is an infrequent occurrence seen in infants with a clinical course compatible with the disease.[11] If the primary event is atelectasis with the membrane being formed later, it would be anticipated that some might die before the membrane had developed.

Certain clinical features of hyaline membrane disease could be explained if the disease results from the absence of a surface-active material:

1. The disease has not been described in stillborn infants. The surface forces at an air-fluid interface could not operate before the first breath.

2. The symptoms may begin within the first few minutes after birth, but often do not become severe until several hours later; death or recovery usually ensues in 4 to 72 hours. Although a normal initial expansion of the lungs would be expected, it would take time for the subsequent mechanical difficulties to be evident. If maturation of the lung lining occurred in the first few days of extrauterine life, recovery would be expected.

3. The disease is more common the more premature the infant.[12] Since our data suggest the normal surface behavior usually appears in infants of about 1,100-1,200 gm., its absence from the lungs of certain infants weighing more than this could be an instance of delayed appearance of the normal lung lining material, and more likely the more premature the infant. One could ask if the absence of a specific surface-active material in the lung predisposes to hyaline membrane disease, why do not all infants under 1,100-1,200 gm. (lacking the material) have the disease? The nine such infants thus far studied showed surface tensions similar to those from infants with the disease, but four of the nine were stillborn and two lived only minutes (Fig. 3). In the three who lived more than four hours, long enough to have signs of the disease, the lungs were indeed atelectatic, although there were no membranes. In any case, one cannot expect every very small premature infant to have the disease, without assurance that 1,100-1,200 gm. is a sharp zone of demarcation before which surface-active material never appears.

Among the unexplained features of this disease is the high incidence in infants of diabetic mothers. Whether the resemblance of this group of infants to premature in-

fants is sufficient to assign a similar pathogenesis of the disease remains to be seen.

Finally, the hypothesis presented here that the lack of a normal lining material in the lungs of infants would contribute to the atelectasis seen in hyaline membrane disease does not preclude the possible importance of other factors in the pathogenesis. Immaturity of the lung lining may be associated with immaturity in other respects.[13] A combination of deficiencies or external insults may be required for the complete syndrome. Moreover, other properties or functions of the lung-lining layer deserve investigation.

Summary

Recent observations suggest that a low surface tension in the lining of the lung may permit stability of the alveoli at end-expiration. Lacking such a material, the lung would be predisposed to collapse.

Measurements of the surface tension of lung extracts confirm the presence of a very surface-active substance in lungs of infants over 1,100-1,200 gm. and in children and adults. In lung extracts of very small premature infants and infants dying with hyaline membrane disease the surface tension is higher than expected, suggesting that the surface active material is deficient.

The possible role of this deficiency in the pathogenesis of hyaline membrane disease is discussed.

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REFERENCES

1. Pattle, R. E.: Properties, Function, and Origin of the Alveolar Lining Layer, Proc. Roy. Soc. London, Ser. B 148:217-240, 1958.

2. Pattle, R. E.: Properties, Function, and Origin of the Alveolar Lining Layer, Nature, London 175:1125, 1955.

3. Clements, J. A.: Surface Tension of Lung Extracts, Proc. Soc. Exper. Biol. & Med. 95:170-172, 1957.

4. Brown, E. S.: Lung Area from Surface Tension Effects, Proc. Soc. Exper. Biol. & Med. 95:168-170, 1957.

5. Harkins, W. D.: Physical Chemistry of Surface Films, New York, Reinhold Publishing Corporation, 1952, Chap. 2.

6. Stacy, R. W.; Williams, D. T.; Worden, R. E., and McMorris, R. O.: Essentials of Biological and Medical Physics, New York, McGraw-Hill Book Company, Inc., 1955, Chap. 8.

7. Cook, C. D.; Sutherland, J. M.; Segal, S.; Cherry, R. B.; Mead, J.; McIlroy, M. B., and Smith, C. A.: Studies of Respiratory Physiology in the Newborn Infant: III., J. Clin. Invest. 36: 444-448, 1957.

8. Gitlin, D., and Craig, J. M.: The Nature of the Hyaline Membrane in Asphyxia of the Newborn, Pediatrics 17:64, 1956.

9. Gruenwald, P.: Pathologic Aspects of Lung Expansion in Mature and Premature Newborn Infants, Bull. New York Acad. Med. 32:689-692, 1956.

10. Briggs J. N., and Hogg, G.: Perinatal Pulmonary Pathology, Pediatrics 22:41-48, 1958.

11. Potter, E.: Personal communication to the authors.

12. Silverman, W., and Silverman, R.: Letter to the Editor, Lancet 2:588, 1958.

13. Phillips, L. L., and Skrodalis, V.: Fibrinolytic Enzyme System in Maternal and Umbilical-Cord Blood, Pediatrics 22:715-726, 1958.

Coagulation Studies in the Newborn Period

III. Hemorrhagic Disease of the Newborn

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The term hemorrhagic disease of the newborn was introduced by Townsend [1] in 1894 to include a variety of bleeding disorders which occur during this period of infancy unrelated to trauma, infection, or definite disease. The condition was differentiated from hemophilia.

In 1910 Schwarz and Ottenberg [2] reported a prolonged coagulation time in these cases, and two years later Whipple [3] advanced the hypothesis that the condition was due to a lack of prothrombin. Very low values of this factor were reported by Gelston [4] and later by Kugelmass et al.,[5] but in these studies very inaccurate methods were employed.

In 1937 Brinkhous, Smith, and Warner [6] with a two-stage technique showed that the defect of coagulation of normal newborn infants was due to a reduction of blood prothrombin. After this, independent publications from different parts of the world established the value of vitamin K in prophylaxis and treatment of both the milder disorder and the severer hemorrhagic disease.[7-16] Also adequate evidence [17,18] was given to show that very small quantities could achieve the desired prophylactic effect. It was reported at the time that even administration of vitamin K to the mother during labor prevented the fall in prothrombin.[19-23] However, this observation was not confirmed by some workers.[24-26] Further observations soon made it evident that a reduction of prothrombin alone did not explain completely the coagulation defect of the full-term newborn,[14,23,27-29] and even the value of vitamin K in prophylaxis of hemorrhagic disturbances was seriously questioned.[29-32] The influence of such publications has continued until the present time,[33-35] in spite of the massive evidence reported by Dyggve a few years ago.[36,37]

Early doubts as to the existence of additional factors besides hypoprothrombinemia to explain hemorrhagic disease were not backed by impressive facts. Strong positive evidence in this respect was not offered until Randall and Randall [38] demonstrated that the addition of small amounts of stored serum from normal adults, which contains hardly any prothrombin, brought about a marked improvement in the one-stage prothrombin time of newborn fresh plasma. In 1951, Loeliger and Koller [39] reported a decrease in proconvertin (stable factor, Factor VII) in the blood of full-term babies, which was soon confirmed by others.[40-47] The parallel effect of vitamin K on both prothrombin and proconvertin was also demonstrated by two groups of workers.[43,47]

After Van Creveld et al.[48,49] presented evidence of a defect of the first stage of coagulation in prematures, Hartmann, Doris Howell, and Diamond [50] and McElfresh, Sharpsteen, and Akabane [51] reported a decrease of plasma thromboplastic component (PTC) in the serum of normal newborn infants. This was confirmed in cord blood by other workers.[52,53] In a previous publication [54] we also advanced evidence to show that there was a close relationship among these three deficiencies (prothrombin, proconvertin, and PTC) and that they all responded favorably to vitamin K in infants who did not bleed.

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Hartmann, Howell, and Diamond[50] also demonstrated alterations of other factors besides prothrombin, and of the first stage, in true examples of hemorrhagic disease of the newborn. They studied four cases, and these showed extremely low values for the Quick prothrombin activity; prothrombin itself varied between 1% and 6%, and proconvertin was less than 1%; the generation of thromboplastin was practically absent, and the figures for serum thromboplastic activity were down to between 1% and 3%. They considered that the latter disturbance was the most important factor in predisposing to hemorrhage. This article is the only one which has offered positive evidence of the multiple defects characteristic of hemorrhagic disease. Other references,[39-42] which are cited as demonstrating the participation of a marked deficit of proconvertin, refer exclusively to alterations found in normal newborns. The lack of confirmatory data on actual cases of hemorrhagic disease gives an opportunity for speculation and tends to maintain confusion in this field. This has moved our interest in reporting our findings in a larger group of cases investigated with modern techniques. Moreover, some of our recent observations bring up new problems, the solutions of which would lead to a better understanding of the condition.

Material and Methods

The infants included in this study were all born at the Maternity Service of General Calixto Garcia Hospital, which is connected with the School of Medicine of the University of Havana. It is a poorly endowed institution which takes care of charity patients exclusively, receiving women from the poorest classes. During the course of the study vitamin K was not used prophylactically as a routine, and there was a fairly high incidence of hemorrhagic disturbances independent of severe trauma, accident or obvious disease even in term babies.

During the 32-month period (Dec. 1, 1955, to Aug. 1, 1958) in which the present

TABLE 1.—*Cases of Hemorrhagic Disease of the Newborn*

No.	Date	Race	Sex	Wt. Gm.	Clinical Syndrome	Time After Birth, Hr.	Outcome
1	3/21/56	C	M	2,620	Hematemesis—mediastinal hematoma—fatty liver	30	D
2	4/12/56	C	F	3,650	Melena	55	R
3	6/24/56	C	M	2,255	Umbilical hemorrhage	36	R
4	9/14/56	C	M	4,010	Giant cephalhematoma	AB	R
5	9/21/56	W	M	2,255	Melena	72	R
6	11/25/56	W	M	2,375	Hematemesis	34	R
7	9/27/57	C	F	3,220	Melena	72	R
8	10/7/57	C	M	4,730	Epistaxis	36	R
9	11/7/57	C	M	3,840	Epistaxis	31	R
10	2/6/58	W	F	3,700	Hematemesis & melena	24	R
11	2/10/58	C	M	2,960	Epistaxis	37	R
12	2/16/58	W	F	2,745	Melena	42	R
13	2/16/58	C	M	2,860	Hematemesis & melena	30	R
14	2/25/58	W	M	3,460	Multiple hemorrhages	AB	D
15	3/14/58	C	F	4,725	Giant cephalhematoma	60	R
16	4/4/58	C	M	3,200	Epistaxis	18	R
17	7/29/58	C	F	3,370	Epistaxis	32	R
18	2/24/57	W	F	3,220	Melena	56	R
19	12/3/57	W	M	3,400	Hematemesis & melena	13	R
20	1/20/58	C	M	2,980	Melena	72	R
21	12/2/55	C	F	2,620	Multiple hemorrhages; anoxia	AB	D
22	11/23/56	C	F	2,860	Hematemesis & melena	24	R
23	2/3/57	W	F	3,225	Hematemesis & melena	13	R
24	4/16/57	C	M	3,440	Hematemesis	36	R
25	4/23/57	C	M	3,250	Hematemesis	30	R
26	1/8/58	W	M	2,200	Hematemesis & melena	18	R

R=recovered; D=died; AB=at birth.

study was carried out there have been 26 cases of hemorrhagic syndromes which could be classified as hemorrhagic disease of the newborn out of a total of 8,400 deliveries. This represents an incidence of 1 for every 300 deliveries, which is particularly high, considering that we have excluded visceral hemorrhages in all groups and all cases of bleeding in prematures below 2,250 gm. Clear-cut cases of false melena or hematemesis have also been eliminated.

Of the 26 cases, only 17 had any investigation performed before therapy. However, some of the remaining nine cases illustrate interesting points in relation to this syndrome. The identification of all these patients is tabulated in Table 1. Their birth weight fluctuated between 2,255 and 4,730 gm. Sixteen of them were male and ten female, and seventeen were colored and nine white (the ratio of the population in Cuba is one colored to two white). The syndromes presented by these cases were as follows: hematemesis, 4; melena, 6; epistaxis, 5; hematemesis and melena, 6; giant cephalhematoma, 2; umbilical hemorrhage, 1; multiple hemorrhages, 2.

The time after birth when hemorrhagic manifestations were first noticed was as follows: in the first 24 hours, 9 cases (2 of these at birth); in 24 to 48 hours, 10 cases, and in 48 to 72 hours, 7 cases. Except in one patient (Case 15) treated only by transfusions, all infants received vitamin K (Kapilon *). During the first year of our studies large doses of 10 mg. were given and repeated. Thereafter, smaller doses have been used—never more than 5 mg.; usually 2 to 4 mg. only at the onset. In some patients one-half of the dose was administered intravenously. Blood transfusions were also given in Cases 1, 2, 4, 14, 18, 19, 21, 22, and 23.

The hemorrhagic tendency in three of these patients failed to respond to vitamin K, and was fatal. Of these three patients two came to autopsy; both of them had an extremely severe fatty infiltration of the liver. Two of the three had been subject to severe anoxia during labor and both of them showed marked hemorrhagic disturbances from the time of birth. A brief history of these cases precipitated by severe anoxia follows:

Case 14.—The son of a 25-year-old white primipara was born by cesarean section after a prolonged labor (three days' duration). The amniotic fluid was malodorous and stained with meconium, and the fetal heart became almost inaudible. These signs of serious fetal distress led to the cesarean section. The infant was born asphyxiated, weighing 3,400 gm. It was aspirated and placed in oxygen. There was some improvement, but one hour later he had profuse hemorrhages from the nose and mouth, which recurred several times. The infant became extremely pale, had a continuous monotonous cry, and recurrent attacks of apnea. The heart sounds were feeble and the liver descended 5 cm. below the costal margin. He was given 2 mg. of vitamin K intravenously and a transfusion of 30 cc. of bank blood. An attempt to give a second transfusion two hours later failed because of technical difficulties. The infant died 14 hours after birth. Autopsy was not permitted. The laboratory findings were as follows: bleeding time 20 minutes, coagulation time (Lee-White) 25 minutes. Capillary resistance with the Petechiometer was positive at a pressure of 30 cm.; with a negative pressure of 20 it was negative. The plasma recalcification time was 300 seconds with a negative test for anticoagulants (90 seconds). The one-stage prothrombin time was very prolonged (91 seconds). Proaccelerin (labile factor) was 15.5 seconds (100%) but proconvertin (stable factor) was absent (0%) (time 180 seconds). The serum was kept in refrigerator and a thromboplastin generation test was performed 36 hours later. There was practically no thromboplastic activity.

Case 21.—The son of a colored 36-year-old primipara was born on Dec. 3, 1955, by cesarean section performed because of a difficult delivery with procedentia of an extremity. The mother had syphilis which had been treated by penicillin. The infant was born in a very poor condition with large cephalhematomas, generalized cyanosis, and bloody vomitus; he had recurrent attacks of apnea. The weight was 2,920 gm. There was a marked hypotonia and the Moro and grasping reflexes were poor. The sucking reflex was present. There were diminished resonance and numerous fine and course rales and ronchi throughout the lung fields. The heart sounds were good, and the frequency was 108/min. The liver was slightly enlarged. The bleeding time was 17 minutes, and there was

* 2-methyl-1,4-naphthoquinone, supplied by Glaxo Laboratories.

increased capillary permeability. X-ray of the lungs failed to reveal parenchymatous lesions. The baby was placed in oxygen and given penicillin and streptomycin and 10 mg. of vitamin K (Kapilon) and 100 mg. of vitamin C administered parenterally. The condition of the infant continued to be very poor; he was having convulsions on the left side and profuse bleeding from the mouth and nose.

The bleeding time on the second day continued prolonged (17 minutes) and the coagulation time by the capillary tube method was 16 minutes. The baby died after 46 hours. Autopsy revealed multiple focal areas of hemorrhage in the lungs, bilateral adrenal hemorrhage, and parenchymatous hemorrhage in the medulla of both kidneys. The liver showed a marked fatty infiltration. There were large bilateral cephalhematomas. The brain showed edema and marked congestion.

The rest of the cases were fairly definite examples of hemorrhagic disease of the newborn in which there was no history of trauma, infection, or definite disease that could account for the condition. The two instances of cephalhematoma deserve explanation: there was severe bleeding under the scalp that manifested itself more than 12 hours after birth. The blood collection was not localized under the periosteum, as in the usual type of cephalhematoma, but it took place beneath the fascia as in a caput succedaneum. It is possible that a traumatic factor could have played a part in the etiology, but similar cases have been included in other statistics.[55,56]

Because of the emergency of the condition and the technical difficulties involved it was not possible to study all the cases following a definite predetermined routine. In all of these at least a one-stage prothrombin time and a plasma recalcification time were performed. Many of them had bleeding and coagulation times and proconvertin and

TABLE 2.—*Methods Used and Values Obtained in Normal Adults and in Full-Term Newborn Infants*

Test	Method	Full-Term Controls [44,49]*	Adult Controls
1. Coagulation time	Lee-White	6 min. 28 sec.	5 min. 50 sec.
2. Bleeding time	Duke (standardized stylet)	2 min. 46 sec. (1-8 min.)	—
3. Capillary fragility	Negative pressures of 10 cm. with suction machine [48]—30 cm. Hg. with Petechiometer [49]	Negative (never more than 2 or 3 petechiae)	Positive in 80% (3-5 petechiae)
4. Plasma recalcification time	Macfarlane [41]	144.9 sec. ± 76.5; S. E. ± 6.6 sec.	102 sec.
5. One-stage prothrombin time	Quick [42]	44.1% ± 26.8%; S. E. ± 2.2%	89% ± 11%
6. Proconvertin (stable factor)	Biggs-Macfarlane [43] in Tromexan plasma and Koller's [50] †	32.2% ± 19.9%; 3 days 21 sec. ± 4 sec.	100%; 13.9 sec. ± 0.28
7. Proaccelerin (labile factor)	Stefanini's in stored plasma [45]	77.8% ± 13.7%; S. E. ± 1.8%	100%
8. Platelets	Rees-Ecker modification [46]	289,000	—
9. Serum prothrombin	Stefanini [47]	6.95%	8.65%
10. True prothrombin	Stefanini [47]	22.4 sec. ± 7.5	12 sec.-17 sec. 14.3 ± 0.4 sec.
11. Screening test for anticoagulant	PRT mixture of equal parts normal + patient's plasma [47]	Normal PRT	
12. Fibrinogen	Gravimetric procedure [44]	355 ± 88.5 mg.	—
13. Thromboplastin generation test	Biggs-Douglas [44]	54-30-23-22 sec. 7%-12%-18%-20% With vit. K 43-15-12.2-13.1 sec. 8%-54%-70%-65%	30-10-11-11.9 sec. 12%-92%-85%-80%

* These values obtained in our Service refer to infants who had not received vitamin K.
† Reagent supplied by Roche Laboratories.

proaccelerin (stable and labile factor) determinations, platelet count, determination of capillary fragility and the thromboplastic activity of the serum. A complete thromboplastin generation test with various mixtures was performed in only one case. The thromboplastic activity of platelets was studied in four infants. In two of these cases, a semiquantitative method previously described[57] was employed. Fibrinogen, true prothrombin, prothrombin consumption, and screening tests for anticoagulants were also studied in some cases. The methods used and the values obtained in normal adults and in full-term newborns in our service are tabulated in Table 2. In the last six patients a careful follow-up was carried out. Also the effects on thromboplastic activity of mixtures with normal serum, with serum of infants who were not bleeding, and with that of a typical case of hemophilia B were investigated. Different proportions of various sera were usually employed following the suggestions of Biggs.[70] For comparison, sera of newborns with marked hypoprothrombinemia were studied. Also mixtures of sera of infants with hypoprothrombinemia and from patients under the effect of coumarin compounds were investigated by means of the thromboplastin generation test, and the determination of proconvertin.

All the tests in infants were performed with venous blood, drawn with a modified two-syringe technique, using the procedure devised by one of us (V. L. B.[71]). The value of the method in these cases of hemorrhagic tendency was inestimable, and without it we could never have obtained safely the blood necessary for these investigations. Any deep vein puncture would represent a tremendous risk in these infants.

Results

Alterations of the Coagulation and Bleeding Time (Table 3).—The clotting time before treatment was performed in nine cases. It was definitely altered in all but one case, in which the value was 11 minutes.

TABLE 3.—*Coagulation Studies Before Therapy* *

Case No.	Capillary Fragility	Bleeding Time, Min.	Coagulation Time, Min.	PRT, Sec.	One-Stage Prothromb., %	Proconvertin, %	Proaccelerin, %	Platelets (Thousands)	Other Studies
1	--	--	>20	540	<1	0	64	390	SP<2%. Fib. 320 mg.
2	Normal	4.5	11	270	12	--	52	320	Fib. 380 mg.
3	--	3	--	360	3	--	--	--	--
4	Normal	6.5	--	>900	<1	0	10	200	Fibrinog. 160 mg. Anticoag. Neg.
5	--	--	--	480	6.5	--	--	--	Platelet function altered
6	--	--	>25	>900	<1	--	--	--	--
7	--	--	--	120	24	--	--	--	--
8	Normal	2	--	390	2	0	--	276	Platelet function altered
9	--	--	--	>300	1	--	--	--	--
10	Normal	4.5	--	>900	5.5	--	--	--	--
11	Normal	4	23	>900	1.5	--	--	--	Anticoag. Neg.
12	Normal	6.5	>25	270	7.5	3	--	--	Fibrinog. O. K. Anticoag. Neg.
13	Normal	8	>25	420	1	0	--	--	Anticoag. Neg.
14	Altered+	25	>25	300	4	0	100	--	--
15	Normal	6	21	500	3	1.5	80	--	Normal platelet function
16	Normal	5.5	19	254	4.5	0	70	236	Normal platelet function AHG normal PTA altered Prothromb. 32 sec/14 sec.
17	Normal	2.5	--	360	3	0	90	218	AHG normal PTA normal
Mean values		6.2	20	477	4.8	0.5	67	276	

* Except serum thromboplastic activity.
PRT = plasma recalsification time.
SP = prothrombin utilization.

The mean was over 20 minutes. The determinations done with a more sensitive technique, such as the plasma recalcification time, revealed marked alterations in every patient but one, the infant who had a comparatively short one-stage prothrombin time. The mean for the entire group was 477 seconds, which is in sharp contrast with the values observed (144 seconds) in normal newborns who had not received vitamin K.

On the contrary, the bleeding time, although somewhat more prolonged than in normal infants, was within normal limits in 11 out of 13. The only cases showing a marked alteration were the two infants who had suffered from severe anoxia during delivery. Although most infants did not have prolonged bleeding with superficial punctures, when these were deeper, such as venipunctures, bleeding tended to be profuse and persistent, and continued pressure

TABLE 4.—*Serum Thromboplastic Activity (in Per Cent and in Seconds)*

Incubation Time	Before Treatment				After Treatment				Time After Treatment
Case	1 Min.	3 Min.	5 Min.	7 Min.	1 Min.	3 Min.	5 Min.	7 Min.	
5	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	64 sec. 5.5%	42 sec. 8%	21 sec. 23%	22 sec. 18%	4 days
7	66 sec. 5%	58.5 sec. 5.5%	54 sec. 7%	47 sec. 7.5%	31.5 sec. 10%	9 sec. 100%	11 sec. 86%	9 sec. 100%	24 hr.
9	61 sec. 5%	71 sec. 4.5%	63 sec. 5.5%	74 sec. 4.5%	13 sec. 70%	10 sec. 92%	8 sec. 115%	9 sec. 100%	24 hr.
11	90 sec. 3%	90 sec. 3%	82 sec. 3.5%	79 sec. 4%	80 sec. 7%	12 sec. 80%	13 sec. 70%	13 sec. 70%	12 hr.
11					51 sec. 7%	11.5 sec. 84%	11.5 sec. 84%	12 sec. 80%	24 hr.
12	36.5 sec. 6%	29 sec. 13%	29 sec. 13%	34 sec. 10%	38 sec. 8.5%	14 sec. 50%	12 sec. 65%	12 sec. 65%	12 hr.
12					37.5 sec. 8.5%	14 sec. 50%	12.7 sec. 60%	12.7 sec. 60%	24 hr.
13	56 sec. 6%	72 sec. 4.5%	58 sec. 5.5%	73 sec. 4.5%	46 sec. 8%	23 sec. 18%	20 sec. 24%	24 sec. 17%	12 hr.
13					37 sec. 8.5%	13 sec. 36%	14.5 sec. 48%	13 sec. 58%	24 hr.
14	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%					
15	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	90 sec. 3%	5 hr.
15					90 sec. 3%	90 sec. 3%	55 sec. 6%	21 sec. 20%	18 hr.
15					90 sec. 3%	25 sec. 17%	14 sec. 60%	14 sec. 60%	48 hr.
16	60 sec. 5%	66 sec. 4.5%	59 sec. 5.5%	60 sec. 3.5%	90 sec. 3%	80 sec. 3.5%	28 sec. 13%	15 sec. 50%	8 hr.
					75 sec. 4%	46 sec. 8%	32 sec. 10.5%	23 sec. 18%	24 hr.
17	--	71 sec. 4%	79 sec. 3.5%	88 sec. 3%	--	55 sec. 6%	47 sec. 7%	47 sec. 7%	12 hr.
17						54 sec. 6.5%	34 sec. 10%	18 sec. 35%	24 hr.
17						39 sec. 8.5%	11 sec. 80%	11 sec. 80%	48 hr.
18					38 sec. 9%	13 sec. 65%	15 sec. 55%	18 sec. 35%	12 hr.
19					41 sec. 8%	15.5 sec. 48%	16 sec. 45%	19 sec. 30%	12 hr.
20					9 sec. 100%	8 sec. 115%	8 sec. 115%	8 sec. 115%	24 hr.
26					31.5 sec. 10%	9 sec. 100%	11 sec. 86%	9 sec. 100%	24 hr.
26					13 sec. 70%	10 sec. 92%	8 sec. 11%	9 sec. 100%	7 days
Means	4.6%	5%	5.2%	4.8%	18%	48%	53.9%	55.4%	
Infants without hemorrhage	7%	12.5%	18%	20%	8%	54%	70%	65%	

had to be employed in order to prevent the formation of large hematomas.

Alterations of the First Stage of Coagulation.—In every case where the thromboplastic activity of the serum was determined before therapy it was found markedly altered (Table 4). It was always below the mean level of normal newborns who had not received vitamin K therapy. Most cases had a level of 5% or less, and the means for the 10 infants studied were 5%, 4.5%, 5%, and 3.5% at 1, 3, 5, and 7 minutes incubation respectively. In the two cases where a thromboplastin generation test (with all the reagents from the infants) was performed, it was even more abnormal than the serum alone. Also the mixture of serum and barium sulfate plasma which is used to investigated the status of plasma thromboplastic antecedent (PTA) showed a greater degree of alteration (positive test) in Case 16, but it was very similar (negative test) in Case 17. In these two patients the determination of antihemophilic globulin (AHG) was normal. Platelet thromboplastic activity was found abnormal in two and normal in two instances. In Case 8 the alteration, though not severe, was confirmed by a semiquantitative technique. This step has been found somewhat inaccurate in our work with newborns; with the amounts of blood drawn and the high hematocrit value, an insufficient platelet cake is often obtained in spite of a normal count.

The altered thromboplastic activity of serum responded in every instance to vitamin K administration and in 7 out of 10 it reached levels of more than 55% within 24 hours. In two other patients that had not been studied prior to treatment, the serum had reached a normal level of thromboplastic activity within that period. In two more infants only a thromboplastin generation test (TGT) with all the reagents from the patient was performed 12 hours after treatment, and it was still somewhat altered. In Case 16 a part of the abnormality encountered might have been due to the fact that determinations were performed 48 hours after blood was drawn; in all the others, including Case 17, it was performed within this period. In the case treated by transfusion alone also the low values observed could be due to a delay in performing the test. In a recent publication we have reported a loss of thromboplastic activity in the serum stored in glass at 4 C in newborns with very marked alteration of their blood-clotting mechanism.[72]

Thromboplastic Activity of Special Mixtures.—The results of mixtures of normal adult control serum with that from patients with hemorrhagic disease are tabulated on Table 5. The correction of one volume in nine was not marked, but with higher proportions it was very definite. This not only indicates that the serum of these patients does not contain potent antithromboplastic substances, but that the missing factor or factors really exert a quantitative effect (Fig. 1).

Mixtures of the serum of Patients 16 and 17 with that of the patient with hemophilia B (Christmas disease) showed very little

TABLE 5.—*Thromboplastic Generation Test: Mixtures of Normal Serum and That of Patients with Hemorrhagic Disease*

Case	TGT of Serum			10% Normal Serum			50% Mixture		
12	>90	>90	>90	—	—	—	14	13.5	14
13	>90	>90	>90	81	71	59	19	17.5	17.5
14	87	90	90	85	58	47	17	14.5	16
15	>90	>90	>90	90	64	30	10	9	9
16	66	59	80	(20%) 29	12.5	12	—	—	—
				(10%) 56	14.5	17	—	—	—
17	71	79	88	(20%) 41	19.6	14.6	—	—	—
				(10%) 81	52	39.5	20	8.5	11

Results in seconds at 3, 5, and 7 minutes' incubation.

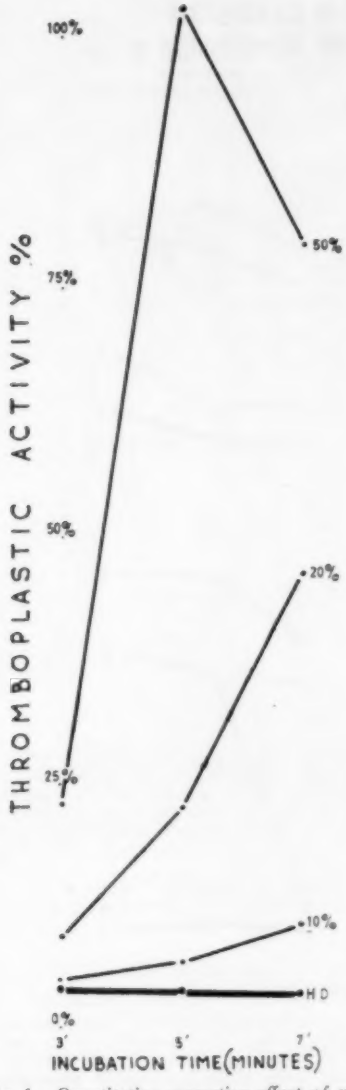


Fig. 1.—Quantitative corrective effect of normal serum on thromboplastic activity of patient with hemorrhagic disease. Of normal adult serum 10%, 20%, and 50% was added to 90%, 80%, and 50% of serum from patient with hemorrhagic disease of newborn. Curve *HD* corresponds to patient's thromboplastic activity.

mutual correction. Before therapy one volume of the Christmas serum did not improve thromboplastic activity when added to nine volumes of the patient's serum. Also the addition of 10% of the latter to 90% of the hemophilia B reagent brought about only a slight increase in activity. Equal volumes of the two sera did not raise thromboplastic activity much above that with the greater defect (Figs. 2 and 3).

After therapy with vitamin K (8-18 hours) thromboplastic activity improved but remained markedly altered. However, these particular sera added to the hemophilic serum brought thromboplastic activity almost to normal. This indicated that PTC deficiency had been totally restored. If this was the case, the remaining decrease of thromboplastic activity must have been due to some other missing factor in the serum.

This was confirmed further by adding one volume of serum obtained after treatment to that of the untreated infant. In spite of the normal PTC content of the former very little correction took place. However, when one volume of a mixture of hemophilic serum and the reagent obtained after treatment were added the improvement was more marked (Figs. 2 and 3).

To test further the possibility of another deficiency of thromboplastic substances several sera from infants who were without hemorrhagic disturbances but who showed a very prolonged microprothrombin determination (method of Lawson [12]) were mixed with Christmas disease serum. The results of these experiments are illustrated in Figure 4.

It can be observed that Patient A also had a lack of PTC, which approached that of the hemophilia B patient. Therefore, this serum was very similar to those of the untreated hemorrhagic disease sera. It should be noted that this case showed the greatest alteration of the plasma recalcification time in this particular group. The other three sera improved markedly when mixed in equal volumes with the Christmas disease serum. However, in Patient B mixtures in other proportions also indicated a fairly marked deficit of PTC. With regard to serum from Cases C and D the improvement brought about in the Christmas disease serum was much greater in all the combinations employed. From these observations it

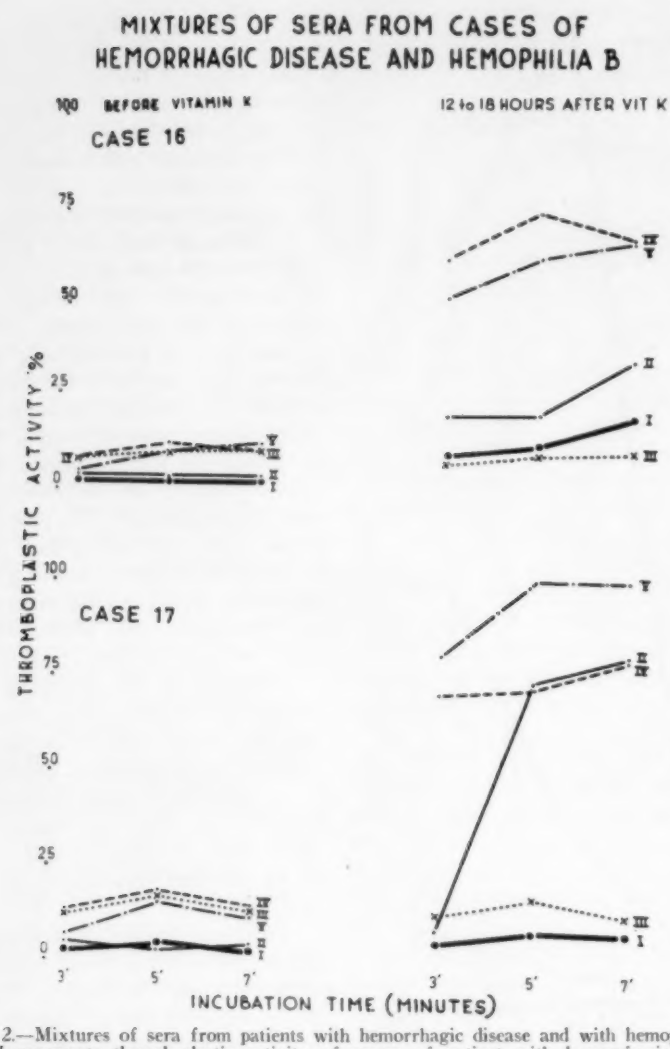

MIXTURES OF SERA FROM CASES OF
HEMORRHAGIC DISEASE AND HEMOPHILIA B
100 BEFORE VITAMIN K
12 to 18 HOURS AFTER VIT K
CASE 16
CASE 17
THROMBOPLASTIC ACTIVITY %
INCUBATION TIME (MINUTES)

Fig. 2.—Mixtures of sera from patients with hemorrhagic disease and with hemophilia B. Curve *I* represents thromboplastic activity of serum of patient with hemorrhagic disease. Curve *III* represents thromboplastic activity of serum of patient with hemophilia B. Curve *V* represents thromboplastic activity of a mixture of equal parts of both. Curve *II* represents activity of a mixture of one volume of hemophilia B serum and nine volumes of serum from a patient with hemorrhagic disease. Curve *IV* represents activity of a mixture of one volume of hemorrhagic disease serum and nine volumes of serum from a patient with hemophilia B. Observe marked increase in corrective effect of serum from patient with hemorrhagic disease on that from patient with hemophilia B after vitamin K administration. This improvement indicates a marked increase in PTC content. Since the thromboplastic activity after therapy continued markedly abnormal, this must have depended on the lack of another factor.

can be seen that the deficiency of PTC varies considerably even in cases of severe hypoprothrombinemia, but that it is usually less severe than in hemorrhagic disease (Fig. 5). Since all the sera were practically devoid of thromboplastic activity, some other defects must have been present.

When serum from infants with such a marked deficiency of thromboplastic activity was mixed with equal quantities of

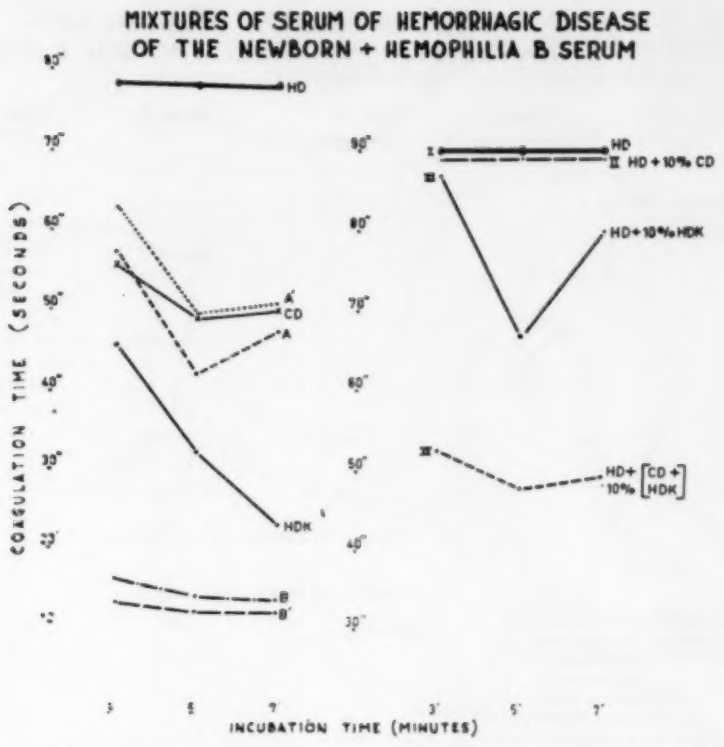
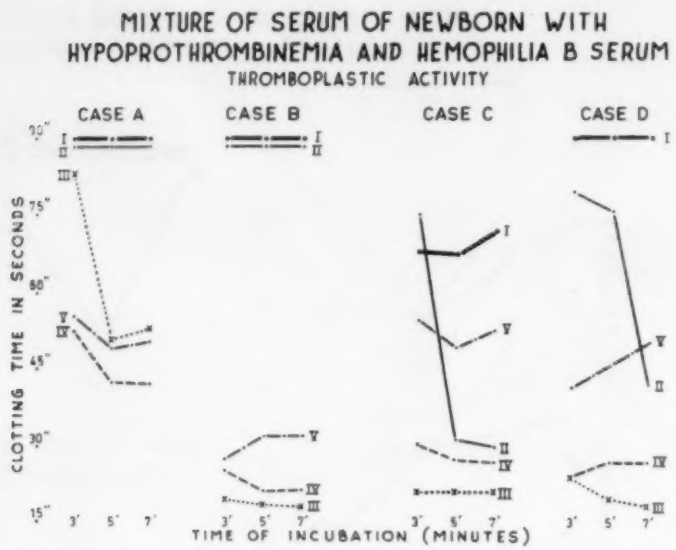


Fig. 3.—Mixtures before and after vitamin K administration reported in seconds *HD:* thromboplastic activity of serum from a patient with hemorrhagic disease. *HDK,* results after vitamin K administration. *CD,* case of hemophilia B. *A'* is a mixture of one part of hemorrhagic disease serum and nine of hemophilia B serum. *A* is a mixture of equal parts. *B* illustrates results of equal amounts of hemophilia B serum with that from treated patient, and *B'* is a mixture of 10% of serum from the infant after therapy with 90% hemophilia B serum.

On the right it can be observed that a mixture of equal parts of hemophilia B serum and that from the patient after therapy brought on a greater correction than either alone. This is indicative of a mixed thromboplastic defect.

serum from the untreated cases of hemorrhagic disease, no improvement took place. This was true with six different sera. In view of the differences in PTC content, it suggests that they must have other severe defects which are common to both. There must be at least two marked thromboplastic deficiencies: PTC and some other yet unidentified thromboplastic factor. In all these experiments barium sulfate plasma from a normal adult control has been employed, which provides an excess of PTA; consequently this particular deficiency is not due to this factor or to any other of the thromboplastic agents which are not adsorbed by barium sulfate. It has to be due to deficiency of an adsorbable factor.

The serum of patients under anticoagulant therapy with coumarin compounds after several days develops a complex mixed defect of the first and second stages of coagulation.[73,74] In our experiments mixing coumarin sera (ethyl biscoumacetate [Tromexan] and acenocoumarol [Sintrom] that had altered thromboplastic activity with the sera of newborns with hypoprothrombinemia (not showing hemorrhagic manifestations) resulted in hardly any correction in the thromboplastin generation test (Table 6). Proconvertin of newborn was



OTHER LABORATORY DATA:				
ONE STAGE PROTHROMBIN TIME (QUICK)	7%	9.5%	11%	4.8%
PLASMA RECALCIFICATION TIME	300"	223"	230"	268"
PROCONVERTIN	48"/13"	54"/12"	30"/13.8"	108"/14"
PROACCELERIN	–	19.5"/17"	22"/20"	18.5"/19.5"
TRUE PROTHROMBIN	–	45"/17"	27"/17"	–
AGE OF INFANT'S SERUM	<12 Hr.	12 Hr.	2 d.	2 d.
AGE OF HEMOPHILIA B SERUM	14 d.	5 Wk.	2 d.	2 M.

Fig. 4.—Corrective effect of sera from infants with hypoprothrombinemia on thromboplastic activity of hemophilia B serum. Curve *I* corresponds to infant's serum. Curve *III* corresponds to serum from patient with hemophilia B. Curve *V* corresponds to equal amounts of both. Curve *II* corresponds to one volume of hemophilia B serum and nine of patient's. Curve *IV* corresponds to one volume of patient's serum and nine of hemophilia B serum. Observe differences in corrective effect.

partly corrected with an equal quantity of serum of patients receiving anticoagulants for only three or four days; when serum of patients under prolonged coumarin therapy was employed, pratically no correction took place (Table 7). This indicates that the defect of the first stage is very much the same in both instances. Moreover, they both exerted similar effects on the serum of the patient with hemophilia B.

Alterations of the Second Stage.—In all but two of the 17 patients studied before the onset of therapy the one-stage prothrombin activity was markedly reduced. These two infants had values of 24% and 12% respectively, which are often encountered in newborns who show no hemorrhagic disturbances. However, the mean for the entire group was 4.8%, and in 10 of them a level of 3% or less was obtained (85 seconds or more). True prothrombin was determined in only one instance and it was well below normal, but the reduction was not quite as marked at this. On the other hand, proconvertin (stable factor) was practically absent in the plasma and sera of every one of the nine infants so tested. The highest value obtained for this factor was 3% and the mean for the group was less than 1%.

Proaccelerin (labile factor) was fairly normal in four patients, definitely reduced in two, and markedly diminished in one case. Hence, although variations may be

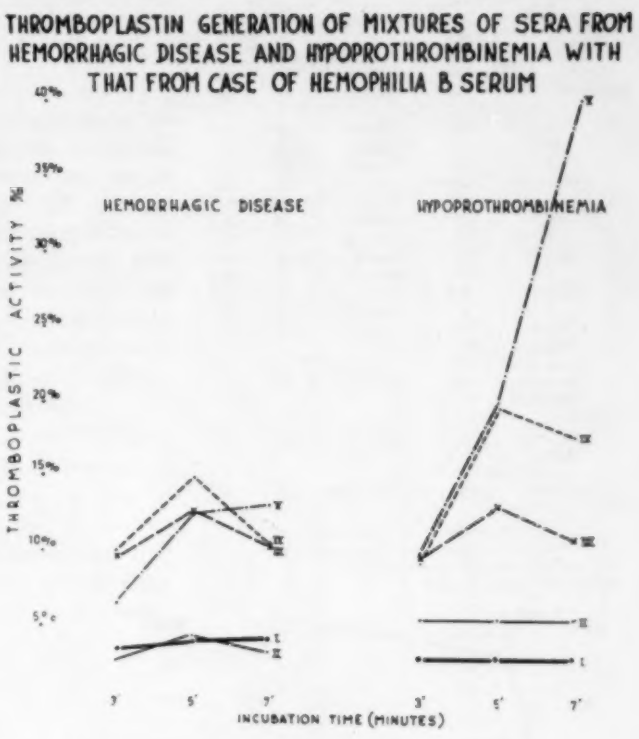


Fig. 5.—Observe greater corrective effect on the thromboplastic activity of serum from a patient with hemophilia B produced by serum from a patient with hypoprothrombinemia without hemorrhagic disturbances, than by that from a patient with hemorrhagic disease of newborn. Curves are identified as in Figures 2 and 4.

TABLE 6.—*Thromboplastin Generation Test of Mixtures of Serum from Newborns and from Patients Receiving Coumarin Drugs*

Mixture	STA Newborn	STA of Patient under ACT	Equal Amounts	10% Infant 90% ACT	90% Infant 10% ACT	Infant and Christmas	ACT and Christmas
T1+52	90-90-90	90-78-30	90-90-90	60-33-33	76-76-47	28-24-29	21-21-20
T2+61	57-41-36	26-18-19	37-24-20	31-19-20	60-50-41	—	—
T2+64	64-62-56	26-18-19	46-29-23	—	—	—	—
T2+70	70-66-70	26-18-19	38-22-20	—	—	—	—
T2+71	64-38-23	26-18-19	41-19-16	—	—	—	—
S1+72	62-61-68	52-41-20	47-44-32	48-40-25	67-77-61	—	—
S2+72	62-61-68	49-32-18	52-16-16	—	66-69-73	—	—
T3+72	90-90-90	46-27-23	87-69-62	—	90-87-85	23-19-18	12-23-19
S2+72	90-90-90	90-90-90	90-90-80	90-90-90	—	21-19-18	17-16-16
T3+64	90-86-83	46-27-23	81-73-63	—	76-83-79	23-19-18	19-23-19
S3+64	90-86-83	90-90-90	86-90-89	—	—	21-19-18	17-16-16
S4+64	90-86-83	90-89-90	90-90-81	—	—	21-19-18	23-24-23
S5+72	90-90-90	90-62-56	90-90-90	—	—	38-30-26	23-20-22
S5+74	90-90-90	90-62-56	90-90-90	90-90-69	90-90-90	34-30-28	23-20-22
S6+74	90-90-90	36-20-14	60-22-16	—	—	34-30-28	11-11-11
Mean values	79-75-74	58-46-38	72-57-52	—	—	27-23-22	19-19-19
Activity (%)	3.5-4-4	5.5-7-9	4.5-5.5-6	—	—	15-20-22	31-31-31

ACT = Anticoagulant therapy.
S = Sintrom (acenocoumarol).
T = Tromexan (ethyl biscoumacetate).
Numbers represent different cases.
Christmas: Hemophilia B serum: (43-46.5-50) (8%-7.5%-7%).
STA: Serum thromboplastic activity.
Results in seconds at 3, 5, and 7 minutes' incubation.

TABLE 7.—*Proconvertin Time of Newborns and of Patients Under Anticoagulant Therapy*

Exper.	No. of Cases	Mean Proconv. Time, Sec.	Anticoagulant & Time Employed	Proconv. Time, Sec.	Mixture
1	7	43	TR-3 d.	35	24
	Control	12	(Same)	35	11
2	2	61	TR-4 d.	42	35
	Control	12.6	(Same)	42	14.5
3	9	46	DIC-3 d.	42	25
	Control	13	(Same)	42	13.8
4	9	54	DIC-3 d.	31	31
	Control	14	(Same)	31	15.5
5	5	68	DIC-3 d.	29	29
	Control	12.6	(Same)	29	12.8
6	4	72	SINT-30 d.	56	60
	Control	12.6	(Same)	56	14
	Means of Exp. 1-5 (32 Cases)	52	DIC & TR	35	28
	Means of Exp. 6 (4 Cases)	72	SINT	56	60
	Means of Normal adult Controls	12.8	TR-DIC-SIM	38	13.6

TR = Tromexan (ethyl biscoumacetate.
DIC = Dicumarol (bishydroxycoumarin).
SINT = Sintrom (acenocoumarol).
PROCONV = Proconvertin.

encountered, a deficiency of this factor is not an outstanding or constant part of the picture of hemorrhagic disease of the newborn.

Results of Other Determinations.—Platelet counts were normal in seven cases, and fibrinogen was also normal in all but one of the few determinations done (that patient had 160 mg. %). Capillary fragility varied in accordance with the bleeding time; both infants with prolonged bleeding time had increased capillary fragility. Serum prothrombin time was performed only once before therapy. It was shorter than that of plasma. Tests for anticoagulants were negative in the five instances in which they were performed.

The mothers of three of the infants failed to show any disturbance of the coagulation mechanism. The one-stage prothrombin time, proconvertin, and the thromboplastin generation of their sera were normal.

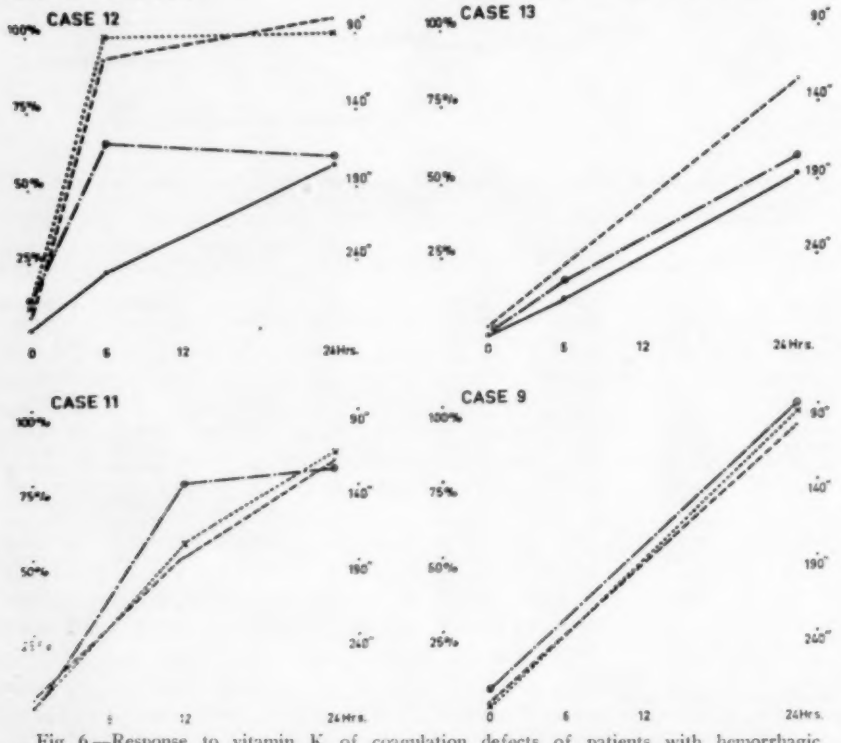


Fig. 6.—Response to vitamin K of coagulation defects of patients with hemorrhagic disease of newborn. Solid line represents proconvertin (stable factor); dash line, prothrombin—one stage (Quick); dotted line, plasma recalcification time; dash-dot line, thromboplastic activity of serum.

TABLE 8A.—*Follow-Up of Clotting Disturbances in Hemorrhagic Disease of Newborn Cases Investigated Before Therapy*

Case	Time, Hr.	PRT, Sec.	Quick, %	Proconvert., %	Prooceler., %	Serum Thromboplastic Activity, Sec.			
2	BT	270	12	—	52		—		
	36	90	80	—	—		—		
	72	92	96	—	100		—		
4	BT	900	1	0	10		—		
	24	90	48	—	—		—		
5	BT	480	6.5	—	—	90	90	90	90
	72	105	100	—	—	64	42	30	22
8	BT	300	2	0	—		—		
	72	90	114	—	—		—		
9	BT	300	1	—	—	61	70	63	74
	24	90	92	—	—	13	10	8	9
10	BT	900	5.5	—	—		—		
	72	111	10	65	—		—		
11	BT	900	1.5	—	—	90	90	82	79
	12	180	42	—	—	50	12	11	13
	24	120	75	—	—	31	11.5	11.5	12
12	BT	270	7.5	3	—	57	29	29	34
	12	90	92	16	—	38	14	12	12
	24	90	100	65	—	37	14	12	12
13	BT	420	1	0	—	55	72	58	73
	12	—	—	12	—	46	23	20	24
	24	98	60	50	—	37	13	14	13
15*	BT	300	3	1.5	80	90	90	90	90
	5	210	23	4	90	90	90	90	90
	18	130	46	14	105	90	90	55	21
	48	115	70	30	95	90	25	14	14
16	BT	254	4.5	0	70	60	66	59	80
	8	98	22	9.5	60	90	80	28	15
	24	91	100	24	75	75	46	32	23
17	BT	360	3	0	90	—	71	79	88
	12	150	35	15	90	—	55	47	47
	24	130	90	30	110	—	54	34	18
	48	107	98	65	105	—	39	11	11

BT = Before therapy. PRT = Plasma recalcification time. Time = Time after therapy.
* No vitamin K, only blood given.

Effects of Therapy (Tables 8A and 8B; Figs. 6, 7, and 8).—Except in the two infants who had been exposed to severe anoxia and in the additional patient with severe fatty infiltration of the liver, vitamin K brought about a rapid improvement of the hemorrhagic tendency. As previously stated, the cases that suffered from anoxia

TABLE 8B.—*Cases Investigated After Therapy*

Case	Time, Hr.	PRT	Quick	Serum Thromboplastic Activity (Sec.)					Other Determinations
18	6	120	75	TGT	39	13	15	18	SP: 17.5%. Fib.: 600 mlg. Platelets 595,000
19	6	165	54	TGT	41	15.5	16	19	SP: 31%. Plat: 295,000.
20	12	180	160	TGT	81	14.5	11	12	----
	36	120	--			--			----
21	12*	--	--			--			Bleeding time: 17 min. Coagulat. time: 16 min.
22	12*	90	48			--			SP: 20%
23	12*	120	30			--			----
24	6	120	22			--			----
25	12	150	25			--			----
26	6	120	18		31	9	11		Prosce: 100%

Time = time after therapy. PRT = Plasma recalcification time. SP = Serum prothrombin (prothrombin utilization). TGT = Test with all reagents from infant. Sec. = seconds. Fib. = Fibrinogen. Plat. = Platelets. Prosce. = Prosceelerin.
* Blood transfusion given. All have received vitamin K.

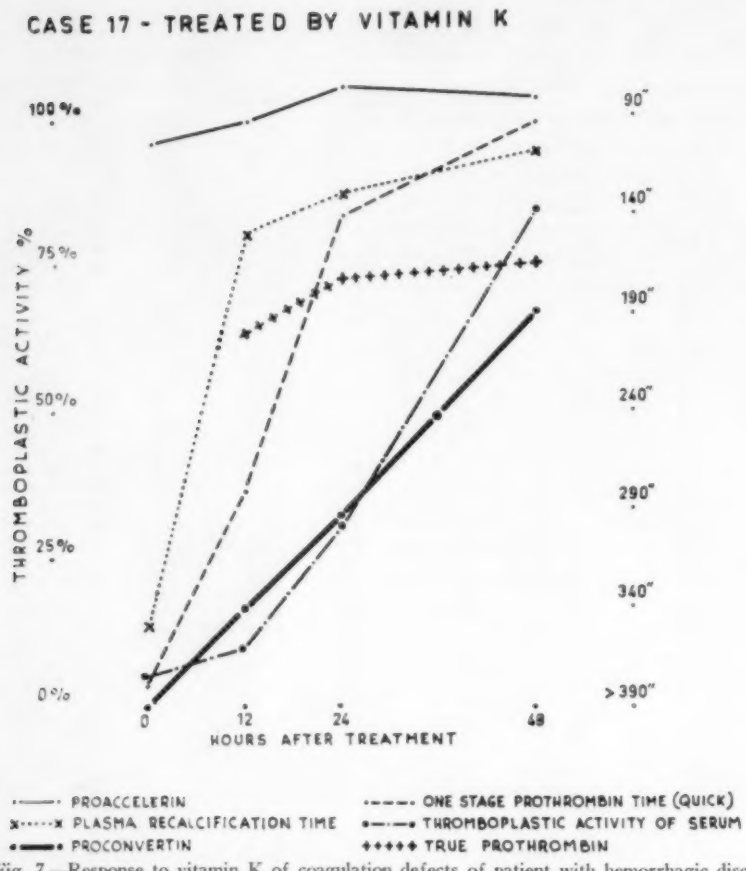


Fig. 7.—Response to vitamin K of coagulation defects of patient with hemorrhagic disease. In this patient response of thromboplastic activity was slower.

showed no improvement, in spite of vitamin K therapy, and severe bleeding continued; it can be recalled that in both of these patients the bleeding time was markedly prolonged and in these there was a positive test for capillary damage. In these infants the plasmatic defects encountered, though refractory to therapy, were fairly similar to those of true hemorrhagic disease. In patients with melena, bleeding from the bowel often continued for several hours after therapy, but in no case was there any persistence after the first 24 hours of treatment. The tendency to bleed from deep punctures subsided in less than three hours.

The coagulation defect always improved with treatment, and most alterations had disappeared completely after 24 to 48 hours. The speed of recovery of the deficiencies present varied in different cases. However, a certain pattern was generally followed. In the first 6-12 hours after vitamin K (alone or combined with transfusions) plasma recalcification time (PRT) and clotting time fell to fairly normal levels in most instances; the mean figures for the former went down from 477 to 132 seconds and only four patients had recalcification time of 130 seconds or more. The one-stage prothrombin time also improved quickly; the per cent activity at the end of this period had gone up to 47.8% from the initial figure of 4.5%. In the two cases in which true prothrombin was determined a fairly high level had been

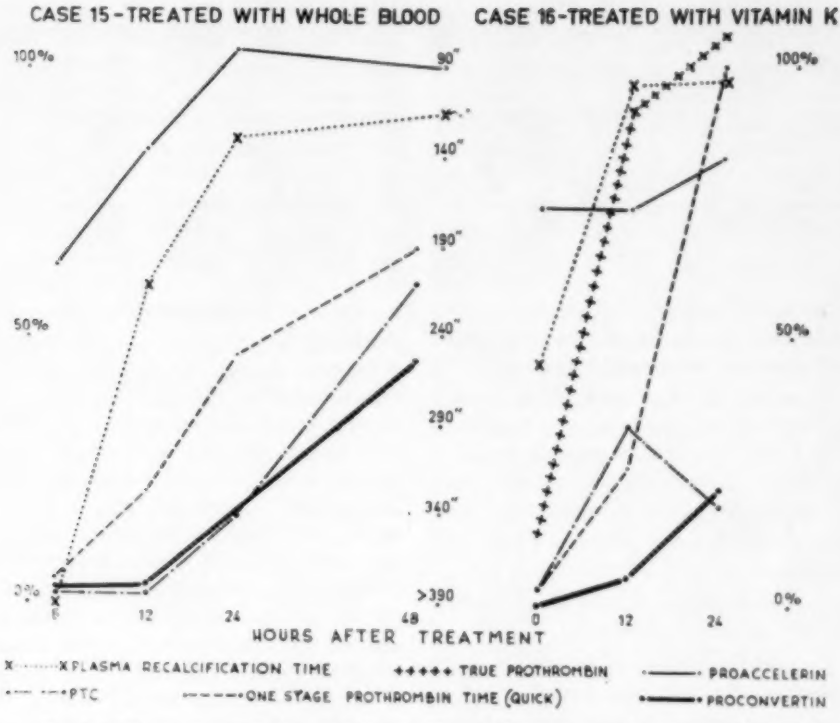


Fig. 8.—Effects of transfusion and vitamin K on defects of coagulation of patients with hemorrhagic disease. Observe rapid response of true prothrombin after vitamin K was administered.

reached within the first 12 hours. Thromboplastic activity reached a fairly high level in four and remained somewhat altered in five (in two of these a TGT with all the reagents from the patient was performed). The persistent alteration, however, did not appear to be in PTC since the most altered sera showed a very marked correction of the defect in serum from a patient with hemophilia B (Figs. 2 and 3).

Proconvertin improved slowly and after 6 to 12 hours the mean level for four cases was still 13%.

After 24 hours the correction was more complete. Plasma recalcification time, one-stage prothrombin activity, and true prothrombin had reached normal levels in most instances. The serum thromboplastic activity was still altered in two cases and it continued abnormal in one more infant even after 72 hours. As previously stated, this alteration appeared to be independent of PTC deficit. The level of proconvertin continued to improve but was still low in half of the cases followed.

All normal levels for the neonatal period [41,45,68,75] were reached within 48 to 72 hours. In the patient treated by blood alone, the rate of improvement was definitely slower (Fig. 8).

Hence prothrombin and PTC deficit and altered coagulation time appear to be corrected more rapidly than proconvertin deficiency and the yet unidentified defect of thromboplastic activity.

An important point in therapy is the use of sufficiently large transfusions in cases of profuse hemorrhage. An anemia of 3,500,000 red blood cells in a newborn probably represents a loss of at least 35%

TABLE 9.—*Transfusion Therapy in Hemorrhagic Disease*

Case No.	4					15			21				
Diagnosis	Giant Cephalhematoma					Giant Cephalhematoma			Melena & Hematemesis				
Weight (gm.)	4,010					4,300			2,860				
Day of birth	1	2	3	4	6	2	2	3	3	3	4	5	7
RBC (millions)	2.6	3.3	3.5	4.2	5.0	2.52	3.8	5.0	1.06	2.9	3.6	3.7	5.3
HGB. (gm.)	8	10.5	11	14	16.5	8.5	13	16	3.5	8.5	10.5	10.7	14.8
Blood given (ml.)	—	120	50	60	—	—	150	60	—	150	120	50	
Total blood given (ml.)	230					210			320				
	57.5/kg.					50/kg.			110/kg.				

of the blood volume. In three of our cases over 50 ml. per kg. in 24 hours had to be used to achieve the desired result (Table 9).

In the present study we have shown that cases of hemorrhagic disease of newborns show a very severe and complex defect in the blood-clotting mechanisms. Newborns not receiving vitamin K exhibit the same disorder, but in a less advanced form. This disturbance is also very similar to that of patients undergoing prolonged administration of coumarin compounds.

The defect consists of a combined deficiency in the first and second stages of blood coagulation. Prothrombin and proconvertin are markedly reduced. The latter reaches values close to zero. This explains the markedly prolonged one-stage prothrombin in time. The thromboplastic activity of the serum is markedly altered, in fact, practically absent, and this depends on the combined deficiency of more than one factor: PTC and at least one unidentified barium sulfate adsorbable substance. The latter defect is very marked, but the deficiency of PTC appears to be more directly proportional to the alteration of the coagulation time and to the tendency to bleed. In accordance with this, patients with hemorrhagic disease seem to have a more marked deficiency of PTC than infants with so-called physiological hypoprothrombinemia. Also in patients with hemorrhagic disease who are improving and whose coagulation time has returned almost to normal, PTC deficit has disappeared in spite of the persistence of other thromboplastic defects.

Comment

Various blood dyscrasias may manifest themselves during the newborn period.[50] The hemophilias and other congenital and hereditary deficiencies of plasmatic factors may produce bleeding in this early period, but this is rare. Cases of congenital thrombocytopenic purpura are also very infrequent, and often occur in infants of mothers who suffer from the disease themselves.[76-78]

The bulk of hemorrhagic disturbances in this early period is precipitated by the hazards of birth, and in these the coagulation defect of the newborn may or may not play a part. However, when no vitamin K is given to the mother or to the infant after birth, and particularly in exclusively breast-fed babies, bleeding unrelated to severe trauma, anoxia, or infection is relatively frequent. This has been the experience in our service. In these cases the disturbance of the blood-clotting mechanism reaches a very marked degree, but usually responds quickly to administration of vitamin K.

Reports of the incidence of hemorrhagic disease vary considerably. Some regard it a very rare condition. Potter,[32] in 13,000 deliveries (half the mothers had not received vitamin K), found no true instance of the disease (the two reported as doubtful were probably not instances of the condition). Sanford et al.[33] reported two in 5,500. Others[56,79] give figures as high as 0.5%-1% of all liveborns. In our service the incidence was about 1 in 300 deliveries, excluding infants with visceral hemorrhages and prematures under 2,250 gm. The differences in the incidence among services not using vitamin K in part depend on the criteria

for diagnosis of hemorrhagic disease. Most authorities tend to follow Townsend's definition and exclude particularly infants that undergo obstetrical trauma. They include internal and external hemorrhages in which no obvious cause is detectable. Others, like Capon,[80] maintain that the diagnosis of hemorrhagic disease should be reserved for cases of external bleeding, such as melena vera, hematemesis, hematuria, and umbilical, mucous-membrane, and vaginal bleeding. He considered internal bleeding in the adrenals, liver, and peritoneal and cranial cavities to be of traumatic origin.

For some authorities [81,82] it is a requisite to have a prolonged coagulation time, while others state that this alteration may or may not be present.[29,56] Most modern authorities have found a very prolonged one-stage prothrombin time, but cases have been encountered in which this alteration was absent.[27,28] Widespread petechial hemorrhage into the brain [56] and retinal hemorrhages [84] have been considered as related to this syndrome. Although they may be related to infantile hypoprothrombinemia, it would be a gross exaggeration to consider them manifestations of hemorrhagic disease of the newborn. The work of Dyggve [30] showed a marked decrease in incidence of most types of hemorrhagic manifestations in infants receiving vitamin K.

In the present stage of our knowledge it is probable that the best criterion is the demonstration of a marked defect of coagulation with the characteristics we have consistently encountered. This defect is similar to that shown by many normal newborns who do not receive vitamin K, but is of a severer degree. The participation of mild precipitating factors, such as minor trauma or low-grade infections, should not exclude the diagnosis.

Infants who undergo severe anoxia may show many alterations similar to those found in cases of hemorrhagic disease, but they exhibit very definite clinical and laboratory differences. Larsen [26] has advanced evidence that anoxia brings about a marked decrease in prothrombin activity. As we have already pointed out, our Cases 14 and 21 belong in this category. In both of them a prolonged bleeding time and a positive test for increased capillary fragility were present. These infants had bleeding which failed to respond to vitamin K. At autopsy in the case in which a postmorten examination was performed there was a marked fatty infiltration of the liver. These two alterations offered a possible explanation for the lack of response and the persistence of the marked hemorrhagic tendency. The relationship of cases of this nature to other instances of hemorrhagic disease is definite; they have in common the extreme prolongation of the one-stage prothrombin time with an almost complete absence of proconvertin (stable factor) and a marked decrease in thromboplastic activity. The important differences are the altered capillary fragility and the prolonged bleeding time resulting from it (the platelets are not reduced in number) and altered liver function caused by hypoxia.

In addition to the diagnostic problem presented by bleeding secondary to asphyxia there are other important circumstances which may cause confusion. In our estimation there are two main reasons for this: (1) errors in diagnosis; (2) failure to appreciate the usual course of the coagulation disturbance of the newborn.

In the diagnosis of melena and hematemesis false diagnoses due to swallowed blood are very common. This has been stressed by Abt,[87] who has shown that as little as 30 ml. of blood introduced in the stomach may give rise to tarry stools, which may continue for as long as 30 hours later. Abt [88] has proposed a simple test for differentiation between melena vera and melena spuria. As we would expect, cases of false hematemesis, melena, or both (both syndromes are frequently associated) do not have as marked an alteration of the coagulation mechanisms and the blood count remains normal.

Malformations are also important causes of hemorrhage from the digestive system, particularly volvulus due to malrotation of

the midgut. We have observed two such instances in the past two years.

Various other rarer conditions may be erroneously taken as manifestations of hemorrhagic disease. Under the circumstances a thorough clinical examination supplemented by the necessary accessory investigations is indicated in any doubtful case, especially one not showing the characteristic alterations of the coagulation mechanism and failing to respond to vitamin K.

The second cause for confusion includes the failure to take into consideration the normal tendency to spontaneous recovery of the clotting defects observed in newborns. This probably explains cases like Nos. 3 and 10, where the one-stage prothrombin time was already improving in spite of the fact that no vitamin K had been administered. On the other hand, in gastrointestinal hemorrhages the persistence of some symptoms after such therapy should not puzzle us since, as has already been stated, blood in the intestines does not begin to be eliminated until 6-8 hours after introduction and may continue to be present in the stools for as long as 30 hours or more.

In some articles [33,35] another factor which does not seem to be properly evaluated is the effect of the infant's diet on the clotting defect of the newborn. Leslie and Sanford [82] reported that, by giving newborns an artificial complementary feeding, hemorrhagic disorders had been eliminated. In agreement with this observation, Solomonsen [89,90] showed that newborns at the breast had more prolonged prothrombin times than those artificially fed, and that this was due to the lower content of vitamin K in human milk. It must be recalled that very small quantities of such a vitamin may prevent physiological hypoprothrombinemia.[17,18] Gellies [91] and more recently Larsen [26] confirmed the lower levels of prothrombin in breast-fed infants.

In the follow-up of our cases the spectacular effect of vitamin K was again observed. This led to a correction of all the disturbances in a relatively short time. In Case 16 the failure of thromboplastic activity to return to nearly normal levels might have depended on a technical error, but even so it was not due to a persistent deficit of PTC. This was corrected completely in 24 hours. The response of the one-stage prothrombin time and plasma recalcification are usually faster than that of proconvertin. The limited data suggest that PTC and true prothrombin also tend to rise quickly, whereas the yet unidentified thromboplastic factor which is missing takes somewhat longer to appear.

The slower and less definite response observed in the patient treated by whole blood alone is in accord with data previously reported. Whipple [3] many years ago recommended the use of blood transfusions in hemorrhagic disease of the newborn, and this led Schloss and Commiskey [92] to try intramuscular blood, which soon became very popular because of its simplicity. However, in 1940 Lawson [12] demonstrated that such therapy was worthless in its effect on prothrombin activity. This was also the experience of Williamson et al.[93] Also MacPherson [94] showed that administration of vitamin K raised the prothrombin quickly, whereas blood transfusion, though it improved the prothrombin index and the coagulation of the blood at first, was followed by a tendency to relapse due to a subsequent drop in prothrombin. In that period one of the few detractors of vitamin K was Scobbie,[28] who even failed to find a prolonged prothrombin time in her patients. Evidently her cases were not true instances of hemorrhagic disease of the newborn. She considered blood transfusion the treatment of choice.

Our point of view coincides with that of Snelling,[15] who considered that blood was indicated when loss had been severe. As already mentioned in the present series, several infants required very large amounts to bring their red blood cells and hemoglobin to nearly normal levels (Table 9). In some of these infants the blood volume seems to be reduced to about 20% or less and this has to be replaced in a comparatively short period. In the treatment of ruptured subcapsular hematoma of the liver we have ob-

tained favorable results in two instances [95,96] with 350 and 500 ml. of blood in less than 12 hours. The recent study of Mason Brown [97] showed that in such a case a loss of about 400 ml. took place into the peritoneal cavity. When these large amounts are lost and replaced, precautions usually followed in exchange transfusions are in order. Citrate tetany and hyperpotassemia from old stored blood must be prevented.

Perhaps the most interesting conclusion derived from this study is related to the nature of the coagulation defects present in these infants. Most authors still consider that low prothrombin and proconvertin are the defects involved; in addition a marked deficit of PTC was shown by Hartmann, Howell, and Diamond.[50] Although these authors were unaware of the complexity of the alterations of thromboplastic activity of serum, our observations are in complete agreement. In fact, the defect in hemorrhagic disease seems to be identical with that of any severe neonatal hypoprothrombinemia except that the quick prothrombin time and proconvertin levels were even lower and the coagulation time was more prolonged. The thromboplastic activity of serum was markedly altered in both, but in those with a more prolonged coagulation time (cases of hemorrhagic disease and case *A*, Fig. 4) the capacity to improve the thromboplastic activity of the serum from a case of hemophilia B was much lower. Much of the decrease of thromboplastic activity of serum of newborns with hypoprothrombinemia appears to be due to the deficiency of a thromboplastic factor or factors yet unidentified. This particular factor could not be PTA,[98] Hagemann factor,[99,100] labile factor,[101] or PTFD,[102] since all these substances are present in excess in the barium sulfate plasma from the normal control used in all our experiments with serum. Hence the particular substance responsible for a part of the altered thromboplastic activity of newborns, which may be corrected by the addition of Christmas disease serum, must be in the fraction which is adsorbed by barium sulfate.

Besides PTC several factors with this property have been described in recent years. The Carr factor,[103] Koller's factor X,[104] the Prower factor,[105] the Stuart factor,[106-108] and a thromboplastic substance described by Greig.[109] Recently, the Prower and Stuart factors have been shown to be the same,[107, 110,111] and Koller et al.[107,112] have been accepted identity between this factor and their factor X. Since very definite differences exist between them, further work is necessary to settle this question. (However, the original description of the latter authors stressed the lability of this substance to storage, which is not the case with the Stuart-Prower factor.) A lack of Stuart-Prower factor has been shown to be entirely responsible for the alteration encountered in many cases previously classified as congenital proconvertin deficiency,[106,110,111] in which there was a coexistent alteration of thromboplastin generation. The defects present in such cases bear a marked resemblance to those encountered in the newborn. The almost complete absence of proconvertin activity in the blood on newborns with severe coagulation defects indicates a marked deficiency of all the substances included in the so-called proconvertin complex (so far proconvertin itself and Stuart-Prower factor). Moreover, a deficiency of Stuart-Prower factor has been demonstrated in the blood of patients receiving prolonged administration of coumarin compounds.[106, 107,113] We have already seen the marked similarity between such a defect and that of neonatal hypoprothrombinemia. Also the lack of effect of fresh blood transfusion on the coagulation defect has been similar in hemorrhagic disease of newborns and in deficiency of the Stuart-Prower factor. All these facts suggest the existence of a deficiency of this factor in the neonatal period.

We have previously stated that the decrease in PTC proper is a most outstanding difference between cases of hypoprothrombinemia that tend to bleed and those without clinical manifestations. It is possible, however, that in some cases a very marked deficit of Stuart-Prower factor may be re-

sponsible for the hemorrhagic tendency. Bachman et al. have shown that 25% of the patients under anticoagulant therapy that had hemorrhagic disturbances had a very marked decrease of PTC; in these cases the level of Stuart-Prower factor remains comparatively high. In another 50% of these cases the opposite was observed; in these there was a predominant lack of Stuart-Prower factor whereas PTC remained between 20% and 40%.

In mixture experiments among several different varieties of secondary hypoprothrombinemia and cases of congenital proconvertin deficiency Biggs[70] has found evidence which indicated the presence of three different thromboplastic deficiencies in the serum alone. These included PTC, Stuart-Prower factor, and possibly factor X. Similar findings have been reported by others.[108] This illustrates the complexity of such mixed defects which bear a marked resemblance to that of newborn infants. Therefore, the need for further work to clear up the problem is obvious.

In some of the cases reported here we have seen that altered platelet function and decrease in proaccelerin may coexist. However, these have been inconstant and usually mild. Their relationship to other abnormalities present is not clear, but their importance is undoubtedly insignificant when compared with the other alterations described. Therefore, we do not think there is reason to consider that decrease in proaccelerin or altered platelet function, as some workers have suggested,[52,114] is primarily responsible for the bleeding tendency in hemorrhagic disease of the newborn.

The widespread use of vitamin K in the newborn has changed what was once a major pediatric problem throughout the world into a matter of only academic interest. This massive experience maintained through more than two decades is of greater value than any statistical analysis in which probably all variables are not known and hence impossible to control. The frequency of hemorrhagic disease when no vitamin K prophylaxis or early feeding was used is evident from this study. The effect of vitamin K in the control of the coagulation disorders is also quite impressive. Therefore, we consider that the occasional article against this practice must be subjected to very critical analysis, lest it may have dangerous consequences.

Summary and Conclusions

A group of 26 cases of hemorrhagic disease of the newborn is reported. The majority of these (17) have been investigated by modern coagulation techniques.

The findings in these cases have been very similar but much severer than those of so-called physiological hypoprothrombinemia of the newborn.

The most outstanding alterations have been an almost complete depletion of proconvertin (stable factor), with a reduction of true prothrombin, and a very prolonged one-stage prothrombin time. The clotting time is prolonged, but the bleeding time is within normal limits. In addition there is a very marked alteration of the first stage of coagulation.

The last-mentioned disturbance consists of a marked decrease in thromboplastic activity of the serum due to a deficiency of several factors. These include PTC and a yet unidentified thromboplastic substance. It is possible that this may be the Stuart-Prower factor.

The same disorders can be demonstrated in infants with severe hypoprothrombinemia who do not show hemorrhagic manifestations. There is suggestive evidence that true PTC deficiency and not loss of thromboplastic activity of serum is related to the prolonged coagulation time and the tendency to bleed.

The clotting defect in the newborn is very similar to that produced by the prolonged use of coumarin drugs.

The alterations encountered in hemorrhagic disease of the newborn respond spectacularly to vitamin K administration. If blood loss is severe, massive transfusions are imperative.

Several erroneous concepts on this subject which have been responsible for considerable confusion are discussed.

Diagnosis of hemorrhagic disease rests on the demonstration of the characteristic coagulation defect in a very marked degree.

Cases of anoxia complicated by multiple hemorrhages may constitute a separate entity. Alterations of blood clotting identical with those of hemorrhagic disease are present, but because of the marked fatty infiltration of the liver they do not respond to vitamin K. Capillary damage is also an important part of the picture, which greatly aggravates the hemorrhagic tendency. It leads to a positive test of increased fragility and to a marked prolongation of the bleeding time. This variety is often fatal.

The high incidence of hemorrhagic disease when no vitamin K prophylaxis is employed (and when no early artificial or complementary feeding is used) corroborates the advantages of the routine use of this vitamin in the newborn.

In this issue (p. 49) we are publishing the special study on the Stuart-Prower deficiency, which was completed after the termination of this manuscript.

Calle 17, No. 609.

REFERENCES

1. Townsend, C. W.: The Hemorrhagic Disease of the Newborn, Arch. Pediat. 11:559, 1894.

2. Schwarz, H., and Ottenberg, R.: The Hemorrhagic Disease of the Newborn with Special Reference to Blood Coagulation and Serum Treatment, Am. J. M. Sc. 140:17, 1910.

3. Whipple, G. H.: Hemorrhagic Disease: Antithrombin and Prothrombin Factors, Arch. Int. Med. 12:637, 1913.

4. Gelston, C. F.: On the Etiology of Hemorrhagic Disease of the Newborn, Am. J. Dis. Child. 22:351, 1921.

5. Kugelmass, I. N.: The Management of Hemorrhagic Problems in Infancy and Childhood, J. A. M. A. 99:895, 1932.

6. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of the Newborn, Am. J. M. Sc. 193:475, 1937.

7. Waddell, W. W., Jr., and Guerry, D., III: The Role of Vitamin K in the Etiology, Prevention and Treatment of Hemorrhage in the Newborn Infant, J. Pediat. 15:802, 1939.

8. Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn Infant: Prematurity and Vitamin K, Bull. Johns Hopkins Hosp. 63:138, 1939.

9. Dam, H.; Tage-Hansen, E., and Plum, P.: K-avitaminose hos spaede børn som aarsag til hemorrhagisk diathese, Ugesk. læger 101:896, 1939.

10. Nygaard, K. K.: Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn, Acta obst. et gynec. scandinav. 19: 361, 1939.

11. Kato, K., and Poncher, H. G.: The Prothrombin the Blood of Newborn Mature and Inmature Infants as Determined by the Microprothrombin Test, J. A. M. A. 114:749, 1940.

12. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn Infant, J. Pediat. 18:224, 1941.

13. Bruchsaler, F. S.: Vitamin K and the Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, J. Pediat. 18:317, 1941.

14. Toohey, M.: Vitamin K Requirements of the Newborn, Arch. Dis. Childhood 17:187, 1942.

15. Snelling, C. E.: Vitamin K in Hemorrhagic Disease of the Newborn Infant, J. Pediat. 22:27, 1943.

16. Nygaard, K. K.: Prothrombin Deficiency as Cause of Hemorrhagic Diathesis in the New-Born, Nord. med. 7:1535, 1940.

17. Sells, R. L.; Walker, S. A., and Owen, C. A.: Vitamin K Requirement of the Newborn Infant, Proc. Soc. Exper. Biol. & Med. 47:441, 1941.

18. Hardwicke, S. H.: Studies on the Minimal Effective Dose of a Water-Soluble Vitamin K Substitute in the Prevention of Hypoprothrombinemia in the Newborn Infant, J. Pediat. 24:259, 1944.

19. Fitzgerald, J. E., and Webster, A.: Effect of Vitamin K Administered to Patients in Labor, Am. J. Obst. & Gynec. 40:413, 1940.

20. Mull, J. W.; Bill, A. H., and Skowroska, H.: Effect on Newborn of Vitamin K Administered to Mothers in Labor, J. Lab. & Clin. Med. 26:1305, 1941.

21. Bohlender, G. P.; Rosenbaum, W. M., and Sage, E. C.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency of the Newborn, J. A. M. A. 116:1763, 1941.

22. Valentine, E. H.; Reinhold, J. G., and Schneider, E.: The Effectiveness of Prenatal Administration of 2-Methyl 1-4 Naphthoquinone in Maintaining Normal Prothrombin Levels in Infants, Am. J. M. Sc. 262:358, 1941.

23. Hellman, L. M., and Shettles, L. B.: The Prophylactic Use of Vitamin K in Obstetrics, South. M. J. 35:289, 1942.

24. Fiechter, N.: Hypoprothrombinämia und Hämorrhagische Diathese des Neugeborenen und

ihre Beziehungen zum Vitamin K, Monatsschr. Geburtsh. u. gynäk. 111:1, 1940.

25. Gasser, E.: Die Hypoprothrombinämie und die K Vitamin Prophylaxis, Arch. Kinderh. 129: 161-243, 1943.

26. Larsen, E. H.: Svingningernei Prothrombinaktiviteten hos nyfødte, Copenhagen, Ejnar Munksgaards Forlag, 1952.

27. Parmelee, A. H.: Hemorrhagic Disease of the Newborn, J. Mich. M. Soc. 42:455, 1943.

28. Scobbie, E. B. S.: Haemorrhagic Disease of the Newborn, Arch. Dis. Childhood 17:175, 1942.

29. Grossman, A. M.: Vitamin K for the Pediatrician, J. Pediat. 19:205, 1941.

30. Sanford, H. N.; Shmigelsky, I., and Chapin, J. M.: Is Administration of Vitamin K in the Newborn of Clinical Value? J. A. M. A. 118:697, 1942.

31. Parks, J., and Sweet, L. K.: Does the Antenatal Use of Vitamin K Prevent Hemorrhage in the Newborn Infant? Am. J. Obst. & Gynec. 44:432, 1942.

32. Potter, E. L.: The Effect on Infant Mortality of Vitamin K Administered During Labor, Am. J. Obst. & Gynec. 50:235, 1945.

33. Sanford, H. N.; Kostalik, M., and Blackmore, B.: Prothrombin Studies on the Blood of Premature Infants and the Value of Vitamin K Therapy, Am. J. Dis. Child. 78:686, 1949.

34. Smith, C. A.: The Newborn Patient, Pediatrics 16:254, 1955.

35. Fresh, J. W.; Ferguson, J. H.; Stamey, C.; Morgan, F. M., and Lewis, J. H.: Blood Prothrombin, Proconvertin and Proaccelerin in Normal Infancy: Questionable Relationships to Vitamin K, Pediatrics 19:241, 1957.

36. Dyggve, H. W.: Undersøgelser over K-vitaminets betydning for blødninger hos nyfødte, Copenhagen, Nyt Nordisk forlag-Arnold Busck, 1952.

37. Dyggve, H. W.: Prophylactic Treatment with Vitamin K of 11,000 Newborn Infants Compared with 22,000 Untreated Infants, Sixth International Congress of Pediatrics, Zurich, 1950.

38. Randall, A., IV, and Randall, H. P.: Prothrombin Deficiency of Newborn, Proc. Soc. Exper. Biol. & Med 70:215, 1949.

39. Loeliger, A., and Koller, F.: Behavior of Factor VII and Prothrombin in Late Pregnancy and in the Newborn, Acta haemat. 7:157, 1952.

40. De Nicola, P.: Factor VII (SPCA): Its Physiological Significance, Blood 8:947, 1952.

41. Larrieu, M. J.; Soulier, J. P., and Minkowski, A.: Le Sang du cordon ombilical, Études neonat. 1:39, 1952.

42. Owen, C. A., and Hurn, M.: Changes in Blood Coagulation Factors During the First Week of Life, J. Pediat. 42:424, 1953.

43. Van der Mey, C. A. M., and Ens, J. C.: Proconvertin Content in the Blood of Newborn Full-Term Infants, Nederl, tijdschr. geneesk. 98: 1157, 1954.

44. Van Creveld, S.; Paulssen, M. M. P.; Ens, J. C.; Van der Mey C. A. M., and Versteeg, P.: Proconvertin Content in the Blood of the Newborn Full-Term and Premature Infants, Études neonat. 3:53, 1954.

45. Salazar de Souza, C.: Les Alterations de la coagulabilité chez les nouveau ne, Pédiatrie 9:8, 1954.

46. Passaro, G. P.: Prothrombin, Factors V and VII in the Newborn, Arch. ital. Pediat. e puericolt. 17:59, 1955.

47. Douglas, A. S., and Davies, P. L.: Hypoprothrombinemia in the Newborn, Arch. Dis. Childhood 30:509, 1955.

48. Van Creveld, S.; Nagel, C. G. M.; Nijenhurs, J. G.; Miranda, S. I., and Tijon, S.: Thromboplastin Formation in the Blood of the Newborn, Études neonat. 3:135, 1954.

49. Van Creveld, S.; Baker, H.; Niegssigt, I.; Sipkemma, J. J., and Smits, C.: Thromboplastin Formation in the Blood of the Newborn Infant, Études neonat. 3:217, 1954.

50. Hartmann, J. R.; Howell, D. A., and Diamond, L. K.: Disorders of Blood Coagulation During the First Week of Life, A. M. A. Am. J. Dis. Child. 90:594, 1955.

51. McElfresh, A. E.; Sharpsteen, J. R., and Akabane, T.: The Generation of Thromboplastin and Levels of Plasma Thromboplastin Component of the Blood of Infants, Pediatrics 17:870, 1956.

52. Fresh, J. W.; Fergusson, J. H., and Lerois, J. H.: Blood Clotting Studies in Parturient Women and the Newborn, J. Obst. & Gynec. 7:117, 1956.

53. Barkham, P.: Christmas Factor Activity of Cord Blood, Brit. J. Haemat. 2:215, 1957.

54. Aballí, A. J.; López Banús, V.; Lamerens, S., and Rozengvaig, S.: Coagulation Studies in the Newborn Period: Alterations of Thromboplastin Generation and Effects of Vitamin K in Full-Term and Premature Infants, A. M. A. J. Dis. Child. 94:594, 1957.

55. Beveridge, R. S.: Haemorrhagic Disease of the Newborn, Arch. Dis. Childhood 3:29, 1928.

56. Clifford, S.: Hemorrhagic Disease of the Newborn, J. Pediat. 14:333, 1939.

57. Rozengvaig, S.: Alteraciones de la prueba de la generación de thromboplastina en un caso de leucemia aguda, Rev. cubana pediat. 30:77, 1958.

58. López Banús, V., and Lamerens, S.: Estudio de la coagulación en el recién nacido a término en nuestro medio hospitalario, Rev. Cubana pediat. 28:381, 1956.

59. Aballí, A. J.; López Banús, V.; Lamerens, S., and Borrajero, I.: Trastornos hemorrágicos en el prematuro, Rev. cubana pediat. 28:651, 1956.

60. Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, Ed. 5, St. Louis, the C. V. Mosby Company, 1956.

61. Macfarlane, R. G., cited by Van Creveld, S.: Blood Dyscrasias with Hemorrhage, in Brenneman's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1948, Vol. 3, Chap. 17.

62. Quick, A.: Quantitative Estimation of Prothrombin, Am. J. Clin. Path. 10:154, 1935.

63. Biggs, R., and Macfarlane, R. G.: Human Blood Coagulation and Its Disorders, Oxford, England, Blackwell Scientific Publications, 1953.

64. Koller, F.; Leliger, A., and Duckert, F.: Experiments on a New Clotting Factor, Acta haemat. 6:1, 1951.

65. Stefanini, M.: Activity of Plasma Labile Factor in Disease, Lancet 1:606, 1951.

66. Leake, C. D., and Guy, E. F.: A Diluting Fluid for Platelet Counting, J. A. M. A. 84:809, 1925.

67. Stefanini, M., and Dameshek, W.: The Hemorrhagic Disorders, New York, Grune & Stratton, 1955.

68. del Bono, N., and Pasaro, G. P.: Metodologie per lo studio delle diatesi emorragiche, Quad. coag. (fasc. 3) p. 96, March, 1956.

69. Biggs, R., and Douglas, A. S.: The Thromboplastin Generation Test, J. Clin. Path. 6:23, 1953.

70. Biggs, R.: Observations on Factor VII Deficiency, Brit. J. Haemat. 2:412, 1956.

71. López Banús, V.: A Simple Method to Obtain Venous Blood Samples from Premature and Newborn Infants, A. M. A. J. Dis. Child. 94:31, 1957.

72. Aballí, A. J.; Rozengvaig, S.; López Banús, V.; Lamerens, S., and Arrastia, F.: Estudios de la coagulación en el recién nacido: II. Peculiaridades de la actividad tromboplástica del suero, Rev. cubana pediat. 30:337, 1958.

73. Douglas, A. S.: Mode of Action of Coumarin Drugs, Brit. M. Bull. 11:35, 1953.

74. Naeye, R. L.: Plasma Thromboplastin Component: Influence of Coumarin Compounds and Vitamin K on Its Activity on Serum, Proc. Soc. Exper. Biol. & Med. 91:101, 1956.

75. Dyggve, H.: Prothrombin and Proconvertin in the Newborn, Acta paediat. 47:251, 1958.

76. Harrington, W. J.; Sprague, C. C.; Minnich, V.; Moor, C. V., Ahlvin, R. C., and Dubach, R.: Immunologic Mechanisms in Idiopathic and Neonatal Thrombopenic Purpura, Ann. Int. Med. 38: 433, 1953.

77. MacAlenney, P. F., and Kristan, J. J.: Thrombopenic Purpura in the Newborn, Am. J. Dis. Child. 78:401, 1949.

78. Epstein, R. D.; Lozner, E. L.; Cobbey, T. S., Jr., and Davidson, C. S.: Congenital Thrombocytopenic Purpura: Purpura Hemorrhagica in Pregnancy and in the Newborn, Am. J. Med. 9: 44, 1950.

79. Kugelmass, I. N., and Tritsch, J. E.: Prenatal Prevention of Potential Hemorrhagic Disease of the Newborn, J. A. M. A. 92:531, 1929.

80. Capon, N. B.: Hemorrhagic Disease of the Newborn: A Study of 61 Cases, Lancet 1:431, 1937.

81. Rodda, F. C.: Studies with a New Method for Determining the Coagulation Time of Blood in the New-Born, Am. J. Dis. Child. 19:269, 1920.

82. Leslie, E. I., and Sanford, H. N.: Substances Involved in Coagulation of Blood of Newborn, Am. J. Dis. Child. 51:590, 1936.

83. Wille, H.: Influence of Avitaminosis K on Occurrence of Retinal Hemorrhages in the New-Born, Nord. med. (Hospitalstidende) 26:1188, 1945.

84. Koller, F.: Das Vitamin K und seine Klinische Bedeutung, Leipzig, Georg Thieme, 1941.

85. Allen, J. G.: Clinical Value of Liver Function Tests: Review with Special Study of Plasma Prothrombin, Gastroenterology 3:490, 1944.

86. Grossman, B. J.; Heyn, R. M., and Rozenfeld, I. H.: Coagulation Studies in the Newborn Infant, Pediatrics 9:182, 1952.

87. Abt, L.: Melena Neonatorum, J. Pediat. 47:1, 1955.

88. Abt, L., and Downey, W. S., Jr.: Melena Neonatorum: The Swallowed Blood Syndrome, J. Pediat. 47:6, 1955.

89. Solomonsen, L.: On the Prevention of Hemorrhagic Disease of the Newborn by Administration of Cow's Milk During the First Two Days of Life, Acta paediat. 28:1, 1940.

90. Solomonsen, L., and Nygaard, K. K.: The Prothrombin Content in Relation to Early and Late Feeding in the Newborn, Acta paediat. 24:209, 1940.

91. Gellies, S. S., and Lyon, R. A.: The Influence of Diet of the Newborn Infant on the Prothrombin Index, J. Pediat. 19:495, 1941.

92. Schloss, O. M., and Commiskey, L. J. J.: Etiology and Treatment of So-Called Hemorrhagic Disease of the Newborn, Am. J. Dis. Child. 3:216, 1912.

93. Williamson, H. E.; Stadler, H. E., and Owen, C. A.: Curative Effect of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant, Proc. Soc. Exper. Biol. & Med. 47: 116, 1941.

94. MacPherson, A. I. S.: Treatment of Hemorrhagic Disease of the Newborn, Brit. M. J. 2: 433, 1941.

95. Aballí, A. J.; Moreno, O.; Fernandez, M.; Toledo, J., and Borrajero, I.: Hemorrhagia interna por ruptura de hematoma subcapsular hepático en el recién nacido, Rev. cubana pediat. 27:651, 1955.

96. Aballí, A. J.: Reporte del V Congreso Pan Americano de Pediatría: Dos sindromes de interés

médico quirúrgico en el período neonatal, An. Nestlé 65:38, 1957.

97. Mason Brown, J. J.: Hepatic Hemorrhage in the Newborn, Arch. Dis. Childhood 32:480, 1957.

98. Rosenthal, R. L.; Dreskin, O. H., and Rosenthal, N.: Plasma Thromboplastic Antecedent Deficiency, Blood 10:120, 1955.

99. Ratnoff, O. D., and Calopy, J. E.: A Familiar Hemorrhagic Trait Associated with a Deficiency of a Clot-Promoting Fraction of Plasma, J. Clin. Invest. 34:602, 1955.

100. Jim, R. T. C., and Goldfein, S.: Hageman Trait (Hageman Factor Deficiency), Am. J. Med. 23:824, 1957.

101. O'Brien, J. R.: Factor V in Blood Coagulation in Vitro and Report of a Case of Factor V Deficiency, Brit. J. Haemat. 4:210, 1958.

102. Spaet, T. H.; Aggeler, P. M., and Kensall, B. G.: A Possible Fourth Thromboplastic Component, J. Clin. Invest. 33:1095, 1954.

103. McElfresh, A. E.: Deficiency of a Previously Unrecognized Serum Coagulation Factor Occurring in 5 Siblings (Society Transactions), A. M. A. J. Dis. Child. 94:501, 1957.

104. Koller, F.: Le Facteur X, Rev. hémat. 18: 362, 1955.

105. Telfer, T. P.; Denson, K. W., and Wright, D. R.: A New Coagulation Defect, Brit. J. Haemat. 2:308, 1956.

106. Hougie, C.; Barrow, E. B., and Graham, J. B.: Stuart Clotting Defect, J. Clin. Invest. 34: 485, 1957.

107. Bachmann, F.; Duckert, F.; Geiger, M.; Baer, P., and Koller, F.: Differentiation of Factor VII Complex—Studies on the Stuart-Prower Factor, Thrombosis et Diathesis hemorrhagica 1: 168, 1957.

108. Bachmann, F.; Duckert, F., and Koller, F.: The Stuart-Prower Assay and Its Clinical Significance, Thrombosis et Diathesis hemorrhagica 2:24, 1958.

109. Greig, H. B. W., and Tattersal, J. C.: Evidence for the Existence of a Third Serum Clotting Factor, Brit. J. Haemat. 2:421, 1956.

110. Dische, F. E.: Substances with Factor VII Activity, Brit. J. Haemat. 4:202, 1958.

111. Bachmann, F.; Duckert, F.; Fluckiger, P., and Hitzig, W.: An Unusually Severe Hemorrhagic Diathesis, Proc. 6th Congress European Society Haematology, Copenhagen, 1957.

112. Koller, F.; Duckert, F.; Bachmann, F.; Streuli, F., and Geiger, M.: The Differentiation of Serum Clotting Factors, Proc. 6th European Society Haematology, Copenhagen, 1957.

113. Horder, M. H.: Der Stuart Factor Während der Cumarin Therapie, Thrombosis et Diathesis hemorrhagica 2:170, 1958.

114. Van Creveld, S.; Paulssen, M. M. P., and Teng, S. K.: Prothrombin and Accelerator Globulin in the Plasma of Newborns under Normal and Pathological Conditions, Neonatal Studies 1:1, 1952.

Coagulation Studies in the Newborn Period

IV. Deficiency of Stuart-Prower Factor as a Part of the Clotting Defect of the Newborn

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In a previous publication [1] and in the preceding paper [2] we have presented evidence indicating that the serum of newborns with hypoprothrombinemia has a marked deficit of another thromboplastic substance besides PTC. Moreover, in mixture experiments with the thromboplastin generation test and the Loeliger-Koller technique for determination of proconvertin, newborns with severe hypoprothrombinemia appeared to have the same defect as patients receiving prolonged treatment with coumarin compounds. The various deficits of these newborns were corrected by means of stored normal serum.[1,2]

The recently described Stuart factor [3,4] is a stable substance adsorbed by barium sulfate, which participates in the first and probably in the second stage of blood coagulation. Its deficiency is associated with a low thromboplastic activity of the serum and a very prolonged one-stage prothrombin time. The use of Russell viper venom (Stypven) also gives an abnormal result. The determination of proconvertin with a substrate plasma filtered through 30% asbestos shows a marked deficiency. This is due to the fact that this substrate is also devoid of Stuart factor.[3,4] This new coagulation factor has been identified with the Prower factor [5,6] and has since been referred to as the Stuart-Prower factor. Several publications have demonstrated that it is markedly deficient in patients receiving prolonged treatment with coumarin compounds.[3,7,8]

These characteristics made it seem highly probable that the deficient unidentified thromboplastic substance in the serum of newborns with hypoprothrombinemia [2] was the Stuart-Prower factor. Also the known deficit of proconvertin might be due in part to such a deficiency. These speculations made it imperative to attempt a direct demonstration of a deficiency of Stuart-Prower factor in the newborn.

Material and Methods

The newborns utilized for these experiments were all normal infants who did not show hemorrhagic manifestations. Unless otherwise stated, none had received vitamin K. They were between 2 and 3 days of age, and all of them were exclusively breast fed. Those with greater alterations were selected by means of a microprothrombin test.[9]

The Stuart-deficient plasma and serum used in this work were sent to us by Dr. J. B. Graham, of Chapel Hill, N. C., in a lyophilized form. They were obtained from his patients with Stuart-Prower deficiency.

The sera and plasma of the infants were obtained by methods previously described [2,10] on the same day of the experiment. Eight sera from newborns were studied in two groups by means of the thromboplastin generation test. The first day two infants were taken and all the standard mixtures performed. Then the serum was mixed in various proportions (equal amounts, one volume in nine, and nine volumes in one) with that of the Stuart-Prower-deficient serum, reconstituted shortly before this. Also mixtures with hemophilia B serum kept in deep freeze, and with stored adult serum were investigated. The reconstituted serum was kept in the refrigerator at 4 C for 15 hours, and mixed with each one of the sera of the last six infants, obtained 6 hours prior to this. These eight sera,

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and those of four other untreated infants were checked for the proconvertin content by the Loeliger-Koller method, and tests with mixtures of Stuart-Prower-deficient serum or plasma were performed. Five of these cases were also investigated 24 hours after administration of vitamin K. Also mixtures with equal amounts of plasma from a normal adult volunteer who had received bishydroxycoumarin (Dicumeral) for four days were performed. In the latter experiment five of the sera of untreated infants and four sera of those that had received vitamin K were used. We compared the effect of mixing equal volumes of infants' sera with bishydroxycoumarin plasma, and with Stuart-Prower-deficient plasma, as well as with a combination of equal quantities of these two plasmas. This last mixture contained 50% infant serum, 25% Stuart-Prower-deficient plasma, and 25% bishydroxycoumarin plasma.

For a better evaluation other coagulation studies, including the one-stage prothrombin time, true prothrombin, proaccelerin (labile factor), and plasma recalcification time were also performed in the first eight infants. The techniques used in these procedures have already been described in previous publications.[2,10]

In an attempt to determine more directly the status of the Stuart-Prower factor, we attempted a test in which the substrate used was the Loeliger-Koller reagent for proconvertin (supplied to us by the Roche Laboratories), modified by the addition of an equal quantity of the Stuart-Prower-deficient serum (0.05 ml. of each was used). This would correct the deficiency of proconvertin, leaving a substrate devoid of Stuart-Prower factor. However, it is possible that in such a substrate the dilution of proaccelerin (labile factor) and prothrombin may affect the results significantly. For this reason we also tried using a mixture of two parts of the Loeliger-Koller reagent and one part of Stuart-Prower-deficient serum. For comparison the sera of normal adults in various dilutions was similarly treated. The sera from 10 out of the 12 untreated infants and from the 5 patients who had received vitamin K were investigated with at least one of these procedures. To either of these reagents (0.1 ml. of the first one or 0.15 ml. of the second one) we added 0.1 ml. of a one-third dilution of the infants' serum in isotonic saline. This was mixed with 0.2 ml. of a commercial thromboplastin calcium extract (Simplastin) kept at 37 C for three minutes, and the clotting time was determined.

Results

Mixtures in the Thromboplastin Generation Test (Table 1).—The thromboplastin generations of all the infants' sera were abnormal, as was the serum of the Stuart-Prower factor deficiency. The hemophilia B serum was somewhat less altered. Mixtures of equal quantities of serum from the case of Stuart-Prower deficiency and from

TABLE 1.—*Thromboplastin Generation Test of Infants and of Various Mixtures with Stuart-Factor-Deficiency Serum*

Case	TGT of Infant Serum, Sec.			TGT of Stuart-Fact.-Deficien. Serum, Sec.			50% Mixture, Sec.			10% Patient & 90% Stuart, Sec.			90% Patient & 10% Stuart, Sec.		
Time Inc., Min.	3	5	7	3	5	7	3	5	7	3	5	7	3	5	7
1	90	90	90	68	54	45	70	62	60	39	33	23	90	90	90
2	90	90	90	68	54	45	88	67	49	55	41	28	90	90	90
3	77	45	29	56	60	54	45	26	27	—	—	—	—	—	—
4	63	66	53	56	60	54	29	20	24	—	—	—	—	—	—
5	64	37	26	56	60	54	26	22	23	64	36	32	66	18.5	19
6	89	89	79	56	60	54	64	32	34	72	59	37	65	90	90
7	82	90	74	56	60	54	59	26	30	90	55	32	90	82	72
8	90	75	62	56	60	54	42	21	22	—	—	—	—	—	—
Mean	81	71.5	63	59	58.5	52	53	34.5	34	68	42	30	80	74	72
Christmas disease	27	32	32	68	54	45	12	11.5	12	17	15	14	17	15.5	16
Normal adult	8.5	8.5	8.5	56	60	54	9	9.5	8.5	10% Control 19	18	20	10% Control 15	13	13

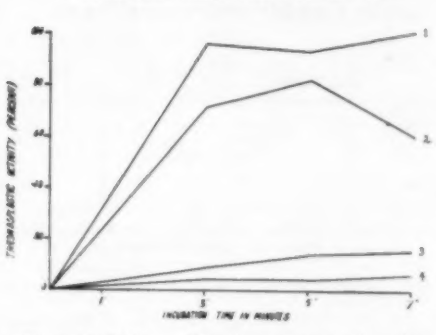
the newborn showed very little cross correction. In contrast the mixtures of the hemophilia B serum with the Stuart-Prower-deficient serum corrected one another almost completely; 50% normal serum added to the Stuart-Prower-factor-deficient serum brought thromboplastic activity almost to normal. The mean values for the eight infants' sera in seconds at 3, 5, and 7 minutes incubation respectively, were 81, 71.5, and 63 seconds, or, expressed in per cent thromboplastic activity, 3.5%, 4%, and 5%. The Stuart-Prower-deficient serum gave clotting times of 59, 58.5, and 52 seconds, or 5.5%, 5.5%, and 6%. The mixture in equal volumes of these sera improved results only to 53, 34.5, and 34 seconds (6%-9% and 9%). In the first two patients who had the severest hypoprothrombinemia there was hardly any cross correction, whereas the other six gave a slight one.

The hemophilia B serum when mixed with the Stuart-Prower-deficient serum improved to 12, 11.5, and 12.5 seconds (65%, 70%, and 60%) and the Stuart-Prower-deficient serum mixed with an equal volume of normal serum to 95%, 90%, and 100%. These results are illustrated in the Figure. The sera of Patients 1 and 2 when mixed with hemophilia B serum showed a partial mutual correction. Serum from Patient 1 when mixed with an equal quantity of the hemophilia B serum had a clotting time of 20, 19, and 18 seconds, and that of Patient 2 had 21, 15.5, and 17.5 seconds. Other proportions showed less mutual correction, indicating that these sera were definitely deficient in PTC, but that another thromboplastic factor was also missing.

The addition of one volume of infant serum to nine of the Stuart-Prower-factor-deficient serum also showed only a slight improvement, whereas 10% Stuart-Prower-factor-deficient serum only brought about some improvement in the mixture with serum from Patient 5. These experiments showed that the loss of thromboplastic activity of these infants' sera was to a large extent dependent on a deficiency of the Stuart-Prower factor, since only a very

TABLE 2.—*Proconvertin Determinations of Infants' Sera and Mixtures with Stuart-Factor-Deficient Serum or Plasma*

Case	Proconvertin Time, Sec.	Stuart-Deficient Reagent, Sec.	50% Mixture, Sec.	Adult Control, Sec.
1	54	41.5	33	12
2	32	41.5	32	12
3	30	33	--	12
4	44	33	--	12
5	81	33	33	12
6	89	33	--	12
7	65	33	--	12
8	24	33	22	12
9	55	43	31	13.5
10	110	43	45	13.5
11	21.5	43	18	13.5
12	101	43	43	13.5
After Vitamin K				
6	39	43	27	13.5
7	40	43	27.5	13.5
9	21.5	43	15	13.5
10	22	43	15	13.5
11	16	43	15.5	13.5
Adult Controls				
Adult plasma	13.5	43	15.5	
Adult serum	13.5	43	15.5	
Adult aged serum and plasma	13.5	43	13.5	
50% Aged serum		43	17.5	
25% Aged serum		43	20	
12.5% Aged serum		43	25	



Thromboplastic activity in per cent of various mixtures. Curve 1 corresponds to a mixture of equal parts of Stuart-Prower-deficient serum and normal adult serum. Curve 2 represents the results obtained with a mixture of 50% Stuart-Prower-deficient serum and 50% of hemophilia B serum. Curve 3 illustrates the mean thromboplastic activity of the sera of the last six infants studied mixed with an equal volume of Stuart-Prower-deficient serum. Curve 4 represents the mean of the thromboplastic activity of the mixtures of equal amounts of Stuart-Prower-deficient serum and the sera of the first two infants investigated.

TABLE 3.—*Proconvertin Determinations of Mixtures of Infants' Serum with Stuart-Prower-Deficient and Bishydroxycoumarin Plasma*

Patient No.	Proconvertin, Sec.	Mixtures with Stuart-Prower, Sec.	Mixtures with Bishydroxycoumarin, Sec.	Mixtures with Stuart-Prower and Bishydroxycoumarin, Sec.
8	24	22	18	18
9	55	31	23.5	18.5
10	110	46	44	30
11	21.5	18	18	--
12	101	43	55	28
After Vitamin K				
6	30	27	22	--
7	40	27.5	24	18.5
9	21.5	15	15	15.5
10	22	15	15	15
Adult Plasma Control	13.5	16	15.5	14.8

little correction or none at all took place when the sera were mixed in various proportions with the serum deficient in such a factor.

Proconvertin (Stable Factor) Determinations.—The sera of the 12 cases investigated before vitamin K therapy showed various degrees of alteration with this test (Table 2), as did the Stuart-Prower-factor-deficient reagent. The serum was used in the first eight; the difference in results from 41.5 to 33 seconds is probably due to activation by contact with glass [11] because of the fact that it was kept in the refrigerator at 4 C for 15 hours. In the last four cases, and in the cases treated with vitamin K Stuart-Prower-deficient plasma was used in the mixtures. In general, there was a mutual correction in all the sera, but only in three of the patients that had received vitamin K did the mixture result in normal control figures. Hence the Stuart-Prower-deficient reagent usually corrected only partially the altered figures of the "proconvertin" test. The mixtures of serum from untreated infants and Stuart-Prower-deficiency sera continued to give very abnormal figures (mean of 32 seconds, or 10%). From these experiments it appears that the altered "proconvertin time" of these infants was generally due to a combination of two deficiencies, proconvertin itself and Stuart-Prower factor. Vitamin K appeared to correct the Stuart-Prower deficiency more quickly than the proconvertin in some cases.

Bishydroxycoumarin plasma after four days is more deficient in proconvertin than is Stuart-Prower-factor-deficient serum.[3,4] Both of the sera showed partial correction when mixed with an equal quantity of infants' serum. The mixture of Stuart-Prower-deficient serum and bishydroxycoumarin plasma showed a marked partial mutual correction. When we mixed the sera of infants with an equal part of such a mixture (50% Stuart-Prower-deficient serum and 50% bishydroxycoumarin) the improvement was more evident than with either one of these alone (Table 3). This result pointed strongly to a dual deficiency.

Stuart-Prower Factor Determination (Table 4).—All the results of observations upon sera of untreated infants were abnormal when compared with normal adult

TABLE 4.—*Stuart-Prower Factor Determination*

Technique A: Substrate: 0.05 ml. of Loeliger-Koller reagent + 0.05 ml. of Stuart-Prower-Factor-Deficient Serum.

	Time, Sec.
Adult Control	20
Newborns, No. 3	31.5
4	50
5	68
6	66
7	58
8	33

Technique B: Substrate: 0.10 ml. of Loeliger-Koller reagent + 0.05 ml. of Stuart-Prower-Factor-Deficient Plasma

Adult Control Serum Dilutions, %	100	50	25	12.5
Time in seconds	11	13	19	25

Newborns, No.	Before Vit. K, Time, Sec.	After Vit. K, Time, Sec.
9	30	13
10	38	15
11	18	16
12	41	--
6	--	22
7	--	22.5

Control Serum 100%; diluted 1/3 in isotonic saline

TABLE 5.—*Various Investigations in Newborns from Present Study*

Patient	Quick, %	Prothrombin, Sec.	Proaccelerin, Sec.	Proconvertin, Sec.	PRT, Sec.
1	9.5	45	19.5	54	225
2	8	42	18	52	260
Control	100	17	17	11	120
3	24	21	20	30	116
4	53	25	19	44	111
5	24	23	21	81	180
6	9.5	28	16	89	118
7	19	27	17.5	65	120
8	42	20	17.5	24	103
Control	92.5	19	19	12	99

serum. The cases that had received vitamin K showed the shortest clotting times, but even some of them were definitely prolonged.

This is additional evidence in favor of a Stuart-Prower deficiency in the newborn infant.

Other Studies

The other tests performed are tabulated in Table 5. These include determinations of one-stage prothrombin, true prothrombin, proaccelerin (labile factor), and plasma recalcification time.

Comment

Mixture experiments with various sera are often subject to errors when storage time is not adequately controlled.[12] For this reason the sera used for the tests of thromboplastic activity were always obtained on the same day of the experiment. The lyophilized Stuart-Prower-deficient serum was reconstituted shortly before the investigations with the first two infants and kept in the refrigerator at 4 C for the following 15 hours for the studies of the remaining six infants. This degree of storage produced some activation of the "proconvertin" content and perhaps contributed to the greater mutual correction found in the second group of experiments (Curve 3, Figure). However, the first two cases showed a much greater alteration of various clotting factors, which would make one expect a greater reduction of the Stuart-Prower factor.

The sera of the first two infants showed only a partial mutual correction when mixed with hemophilia B serum, indicating a definite deficiency of PTC. On the other hand, the Stuart-Prower serum corrected the deficiency of the hemophilia B serum, thus showing a normal content of PTC. Since mixtures of these two sera of different PTC contents showed only a slight degree of mutual correction, they must have another important defect common to both. According to our present knowledge, the Stuart-Prower-deficient serum lacks this factor only.[3-5]

If the loss of thromboplastic activity of these untreated infants was in part due to Stuart-Prower-factor deficiency, then the reduction of proconvertin must also depend at least in part on such a defect. This is in accordance with the results of proconvertin determinations and the mixtures employed. Moreover, the fact that an equal volume of infants' serum with a mixture of bishydroxycoumarin and Stuart-Prower-deficiency sera brought about a much greater improvement than either one of these alone indicates that at least two factors are responsible for the markedly altered results observed in newborn infants.

The test for Stuart-Prower factor, although much rougher, resembles somewhat one recently introduced by Bachmann et al.[7] The Loeliger-Koller substrate is lacking in both Stuart-Prower factor and proconvertin; if 33% to 50% of stable factor (true proconvertin) contained in the Stuart-Prower-deficient serum is added, it can be used to determine the approximate content or activity of Stuart-Prower factor in the sera.

All the infants studied before receiving vitamin K showed a very evident deficiency.

As previously mentioned, the fact that prolonged bishydroxycoumarin therapy brings about alterations, which are almost identical with those of newborn babies, is an additional point in favor of the existence of a Stuart-Prower-factor deficit. Recent work indicates that such patients have a

marked deficiency of this factor.[3,7,8] The same must be true of newborn infants.

Summary and Conclusions

By means of various mixtures of sera subjected to the thromboplastin generation test and the test for determination of proconvertin, we have obtained abundant evidence indicating the existence of a deficiency of Stuart-Prower factor in the serum of newborn infants. This was particularly marked in those infants who had not received vitamin K.

A presumptive test for Stuart-Prower factor was tried, and it also gave abnormal results in every instance. Again it showed the greatest alteration in untreated newborns.

Our data show that a deficiency of the Stuart-Prower factor is an important part of the clotting defect of the full-term newborn.

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REFERENCES

1. Aballí, A. J.; Rozengvaig, S.; López Banús, V.; Lamerens, S., and Arrastía, F.: Estudios de la coagulación en el recién Nacido: II. Alteraciones de la Actividad Tromboplástica del Suero, Rev. cubana pediat. 30:337, 1958.

2. Aballí, A. J.; López Banús, V.; Lamerens, S., and Rozengvaig, S.: Coagulation Studies in the Newborn Period: III. Hemorrhagic Disease of the Newborn, this issue, p. 24.

3. Hougie, C.; Barrow, E. M., and Graham, J. B.: The Stuart Factor: A Hitherto Unrecognized Blood Coagulation Factor—Proc. of the Sixth Congress of the International Society of Blood Transfusions, p. 336, 1958.

4. Hougie, C.; Barrow, E. M., and Graham, J. B.: Stuart Clotting Defect: I. Segregation of a Hereditary Hemorrhagic State from the Heterogenous Group Heretofore Called "Stable Factor" (SPCA—Proconvertin, Factor VII) Deficiency, J. Clin. Invest. 36:485, 1957.

5. Bachmann, F.; Duckert, F.; Geiger, M.; Bear, P., and Koller, F.: Differentiation of Factor VII Complex: Studies on the Stuart-Prower Factor, Thrombosis et Diathesis hemorrhagica 1: 168, 1957.

6. Dische, F. E.: Substances with Factor VII Activity, Brit. J. Haemat. 4:202, 1958.

7. Bachmann, F.; Duckert, F., and Koller, F.: The Stuart-Prower Assay and Its Clinical Significance, Thrombosis et Diathesis hemorrhagica 2:24, 1958.

8. Horder, M. H.: Der Stuart Factor Während der Cumarin Therapie, Thrombosis et Diathesis hemorrhagica 2:170, 1958.

9. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn, J. Pediat. 18:224, 1941.

10. Aballí, A. J.; López Banús, V.; Lamerens, S., and Rozengvaig, S.: Coagulation Studies in the Newborn Period: Alterations of Thromboplastin Generation and Effects of Vitamin K in Full-Term and Premature Infants, A. M. A. J. Dis. Child. 94:589, 1957.

11. Shafrir, E., and de Vries, A.: Studies on Clot-Promoting Activity of Glass, J. Clin. Invest. 35:1183, 1956.

12. Biggs, R.; Sharp, A. A.; Margolis, J.; Hardesty, R. M.; Stewart, J., and Davidson, W. M.: Defects in the Early Stages of Blood Coagulation, Brit. J. Haemat. 4:177, 1958.

Muscular Dystrophy

X. Endocrine and Electrolyte Effects of Methyltestosterone-KCl Therapy

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The administration of methyltestosterone and potassium chloride to patients with muscular dystrophy in an unsuccessful attempt to modify the downward course of the muscle debility provided an opportunity to assess the effects of this androgen upon certain endocrine indices.

Materials and Methods

Clinical and other pertinent data on the 13 boys and 2 men receiving approximately 10 mg. of methyltestosterone as buccal Linguets and 1 to 3 gm. of potassium chloride per os daily for 12 to 24 months have been presented earlier.[1] At the end of the therapeutic trials, and in some instances prior to and during their course, roentgenograms of the sella turcica, the urinary excretion of pituitary gonadotropins,[2] 17-hydroxycorticosteroids,[3,4] and 17-ketosteroids,[5,6] the level of serum protein-bound iodine,[7,8] the blood and serum solutes, and the responses of the blood sugar and serum inorganic phosphorus to dextrose,[9] to insulin,[9] and to epinephrine[10] were examined.

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Endocrine Manifestations

A. Clinical Findings.—The parents of one boy reported the onset of aggressive behavior.

Within two or more months after institution of methyltestosterone therapy voice pitch became lower in all but four of the boys. At the end of 12 or more months of treatment, occasional acne and increased fa-

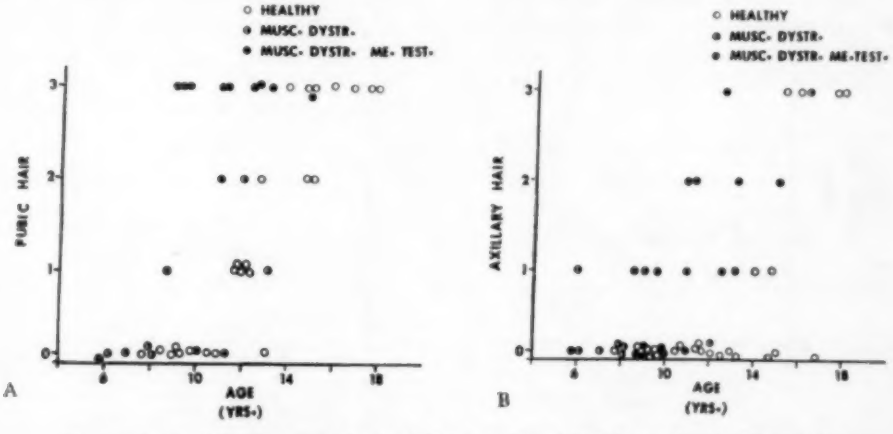

Fig. 1.—Accelerated appearance of pubic (*A*) and axillary (*B*) hair in patients with muscular dystrophy receiving methyltestosterone-KCl. Open circles identify healthy boys, half-closed circles refer to untreated muscular dystrophics, and closed circles refer to muscular dystrophics treated with methyltestosterone-KCl.

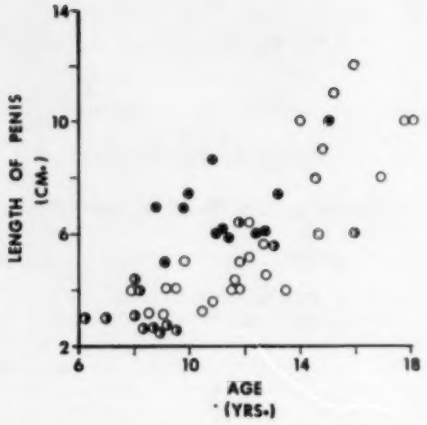

Fig. 2.—Length of penis after treatment with methyltestosterone-KCl. In general the penis was longer in boys receiving methyltestosterone-KCl compared with untreated muscular dystrophics or healthy children. Symbols as in Figure 1.

cial hair, especially on the upper lip and lateral aspects of the cheeks, was present in 9 of the 13 cases. Axillary hair had appeared in seven boys ranging in age from 9 to 12 years, and pubic hair was present in 10 of the 13 (Fig. 1). Gynecomastia of the subareolar button type was noted bilaterally in four of the boys.

In all instances, the parents observed increases in penis size and more frequent erections. Ejaculations were not reported. The size of the penis and of the testes is recorded in Figures 2 and 3. It may be seen that, compared with untreated muscular dystrophics and with healthy children, in treated muscular dystrophics the penis was longer and the maximum diameter of the testis was less.

Both men reported that methyltestosterone treatment had increased the rate of beard growth. There was no change in the decreased libido of one patient or in the decreased frequency of ejaculations in both patients.

1. Sella Turcica: X-rays of the skull obtained at the end of 12 to 24 months of therapy indicated that the sella turcica was within the range of normal in each, a finding which is, of course, also characteristic of those who had not received methyltestosterone.

2. Excretion of Pituitary Gonadotropins in the Urine: The excretion of gonadotropins in the children with muscular dystrophy, which prior to therapy was zero, or virtually zero, remained at these low levels.

3. Indices of Thyroid Function: The serum protein-bound iodine levels decreased by as much as 2.3γ per cent during methyltestosterone therapy, without any clinical

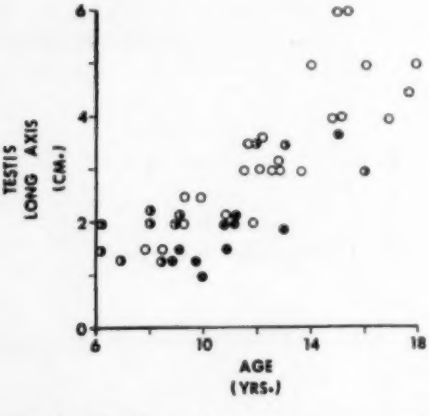

Fig. 3.—The length of the testes after methyltestosterone-KCl therapy. The longer axis of the testis was found to be, in general, less than in the untreated controls. Symbols as in Figure 1.

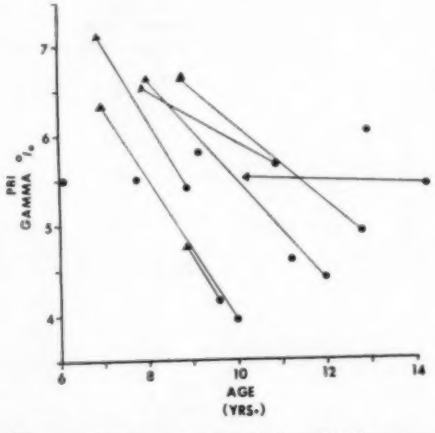

Fig. 4.—Drop in serum protein-bound iodine after methyltestosterone-KCl therapy. Triangles identify pretreatment values, and circles indicate levels at the end of therapy.

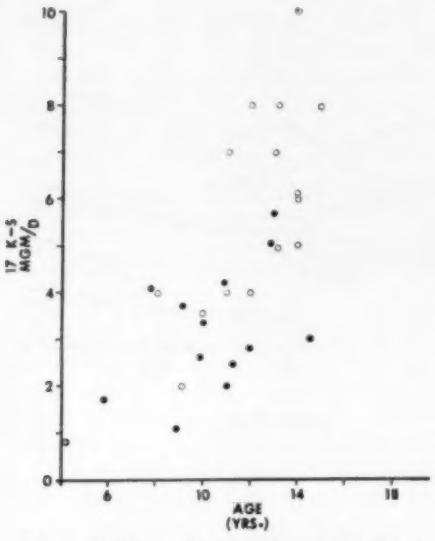

Fig. 5.—17-Ketosteroid excretion in patients with muscular dystrophy treated with methyltestosterone-KCl compared with healthy children. The values are somewhat lower.

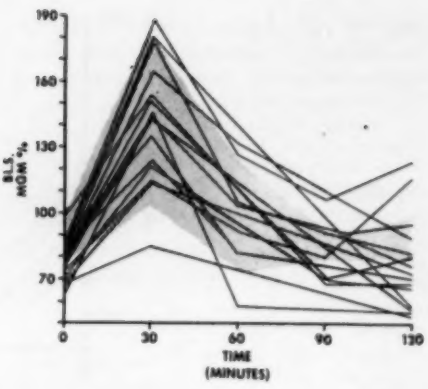

Fig. 6.—Intravenous dextrose-tolerance test in muscular dystrophic children receiving methyltestosterone-KCl. The shaded background indicates responses in 10 untreated children with muscular dystrophy, representing the mean ±1 S. D. There is no evidence that treatment alters the dextrose-tolerance test pattern.

manifestations of hypothyroidism and without significant change in the serum cholesterol levels (Fig. 4).

4. Urinary 17-Hydroxycorticosteroids and 17-Ketosteroids as Evidences of Adrenocortical and Testicular Secretory Activity: At the end of therapy the 24-hour excretion of 17-hydroxycorticosteroids was within the normal range. However, the urinary 17-ketosteroids were less than one would expect in relationship to the age of the individual patients. This finding suggests that methyltestosterone actually decreased the gonadal and/or adrenocortical precursors of the 17-ketosteroids (Fig. 5) since previous studies [6] revealed no difference between healthy and muscular dystrophic children in this regard.

B. Carbohydrate Metabolism.—1. Blood Sugar and Serum Inorganic Phosphorus Changes After I. V. Dextrose Administration 0.5 Gm. per Kilogram of Body Weight: The rise in blood sugar levels one-half hour after the rapid injection of dextrose and the subsequent values were about the same as those reported previously in muscular dystrophics not receiving any medication (Fig. 6).

Decreases in Serum Inorganic Phosphorus One-Half Hour After Dextrose, Insulin, and Epinephrine

Tolerance Test	Healthy Children		Muscular Dystrophy Without Rx		Muscular Dystrophy Methyltestosterone-KCl Rx	
	Mean ± S. D. Mg.%	(No.)	Mean ± S. D. Mg.%	(No.)	Mean ± S. D. Mg.%	(No.)
Dextrose (i. v. 0.5 gm/kg., zero time)	−0.44±0.20	(30)	−0.32±0.25	(23)	−0.59±0.24	(12)
Insulin (i. v. 0.1 unit crystalline rapid-acting commercial insulin/kg., zero time)	−1.29±0.44	(10)	−0.44±0.22	(12)*	−0.25±0.14	(11)*
Epinephrine (s. c. 0.01 ml/kg. of 1:1000 aqueous solution free of arterenol, divided dosage at 0, 10, and 20 min.)	−0.84±0.33	(11) †	−0.26±0.17	(15)*	−0.30±0.25	(10)*

* Statistically significant differences from control values in healthy children.
† Chiefly teen-agers in this group.

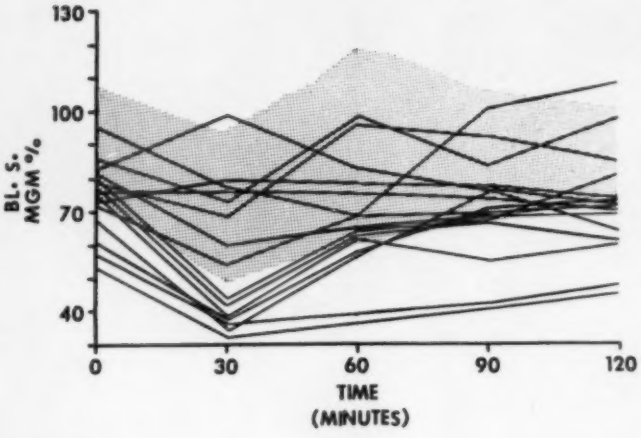

Fig. 7.—Insulin-tolerance studies in treated muscular dystrophics. The administration of 0.1 units of crystalline insulin per kilogram of body weight at zero time produces essentially the same response in the blood sugar of untreated (shaded background represents mean response ±1 S. D.) and treated (individual lines) muscular dystrophics, if allowance is made for the somewhat lower zero values in the treated group.

The serum inorganic phosphorus values were the same as the responses in untreated muscular dystrophics. In both instances, the decrement was about equal to that in healthy children (Table). The recorded differences are not statistically significant.

2. Responses During Insulin-Tolerance Tests: 0.1 Unit of crystalline commercial rapid-acting insulin per kilogram of body weight, administered intravenously at zero time, produced as great a decrement in blood sugar in these children as in healthy controls, if the lower mean sugar value in the former at zero time is taken into account (Fig. 7).

However, as in untreated muscular dystrophy, the usual decrease in serum inorganic phosphorus observed after the intravenous administration of crystalline insulin was less (Table).

3. Epinephrine-Tolerance Tests: Though not shown in a figure, methyltestosterone therapy did not modify the less marked hyperglycemic response to epinephrine characteristic of muscular dystrophy.[10] Thus, at one hour the mean rise in blood sugar in our treated group was only 25.6 mg. % compared to 72.1 mg. % in the healthy controls.

The serum inorganic phosphorus decrement remained within the low range recorded for untreated dystrophics (Table).

Comment

The acceleration of penile growth together with the somewhat smaller transverse diameter of the testes indicates that a mild adrenogenital syndrome had been produced. This was not associated with either a spurt in height or any detectable changes in body configuration, though skeletal age was slightly accelerated.[1]

The failure to observe urinary gonadotropins and the lower than expected urinary 17-ketosteroids in these patients suggest that these quantities of androgen suppressed the anterior pituitary.

The decrease in serum protein-bound iodine presumably reflects a diminution in the binding of thyroxin to α-globulin,[11-13] probably because testosterone evoked its characteristic rise in β-globulin concomitant with a decrease in the α-globulin fraction. Alternatively, the decrease may have resulted from inhibition of pituitary T. S. H. or of the thyroid, or it may represent altered distribution or degradation.

Our studies, in contrast to earlier reports,[14-16] have failed to show any effect of testosterone on carbohydrate metabolism. The abnormalities in the serum inorganic phosphorus responses to insulin and in the blood sugar and serum inorganic phosphorus changes after epinephrine characteristic of muscular dystrophics [9,10] were not altered by

methyltestosterone-KCl therapy. Presumably the disease of the muscles interferes with the disposal of glucose in these tissues in response to insulin and also limits the contribution of the muscle mass to the hyperglycemia and to the decrease in serum inorganic phosphorus induced by epinephrine.

Summary and Conclusions

Boys with juvenile muscular dystrophy treated with methyltestosterone Linguets, approximately 10 mg. per day for 12 to 24 months, together with 3 gm. of potassium chloride per os, developed a mild adrenogenital syndrome as indicated by increased penile length, decreased size of testicles, and slight acceleration of skeletal age without change in body dimensions or configuration.

No measurable gonadotropins were found in the urine of these patients when they reached the age when these hormones are occasionally detectable; this was presumed to represent anterior pituitary suppression by methyltestosterone.

Lower levels of serum protein-bound iodine appeared without clinical or other laboratory evidence of decreased thyroid hormone supplies; this, too, could have been the consequence of suppression of pituitary thyroid-stimulating hormone, but more likely it resulted from decreased binding of thyroxin to serum α-globulin. However, direct effects on thyroidal synthesis of hormone or on its volume of distribution or degradation have not been excluded.

The urinary 17-hydroxycorticosteroids fell within the normal range.

The urinary 17-ketosteroids indicate that the rise which might be expected with age in these children did not occur, and, therefore, a suppressive effect of methyltestosterone can be postulated.

The blood sugar and serum inorganic phosphorus changes after intravenous dextrose, intravenous insulin, or subcutaneous epinephrine were the same as those seen in untreated muscular dystrophics, i. e., the decrease in serum inorganic phosphorus response to insulin remained less than in normals, and epinephrine evoked the lesser degree of hyperglycemia and hypophosphatemia previously described as a characteristic feature of muscular dystrophy; all of these manifestations are presumably attributable to a diminished muscle mass participating in carbohydrate metabolism.

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REFERENCES

1. Van Diermen, J.; Wratney, M. J.; Mateer, F. M., and Danowski, T. S.: Muscular Dystrophy: IX. Body Growth, Muscle Strength, and Serum Solutes During Methyltestosterone-KCl Therapy, A. M. A. J. Dis. Child., to be published.

2. Gorbman, A.: Ultrafiltration of Urine for Collection and Biological Assay of Excreted Hypophyseal Hormones, Endocrinology 37:177-190 (Sept.) 1945.

3. Nelson, D. H., and Samuels, L. T.: A Method for the Determination of 17-Hydroxycorticosteroids in Blood: 17-Hydroxycorticosterone in the Peripheral Circulation, J. Clin. Endocrinol. 12:519-526 (May) 1952.

4. Silber, R. H., and Porter, C. C.: The Determination of 17, 21-Dihydroxy-20-Ketosteroids in Urine and Plasma, J. Biol. Chem. 210:923-932 (Oct.) 1954.

5. Holtorff, A. F., and Koch, F. C.: Colorimetric Estimation of 17-Ketosteroids and Their Application to Urine Extracts, J. Biol. Chem. 135:377-392 (Sept.) 1940.

6. Danowski, T. S.; Bastiani, R. M.; McWilliams, F. D.; Mateer, F. M., and Greenman, L.: Muscular Dystrophy: IV. Endocrine Studies, A. M. A. J. Dis. Child. 91:356-364 (April) 1956.

7. Danowski, T. S.; Johnston, S. Y., and Greenman, J. H.: Alterations in Serum Iodine Fractions Induced by the Administration of Inorganic Iodide in Massive Dosage, J. Clin. Endocrinol. 10:519-531 (May) 1950.

8. Danowski, T. S.; Mateer, F.; Weigand, F. A.; Peters, J. H., and Greenman, J. H.: Serum Iodine Fractions in Subjects Receiving Potassium Iodide in Small Dosage, J. Clin. Endocrinol. 10: 532-539 (May) 1950.

9. Danowski, T. S.; Gillespie, H. K.; Egan, T. J.; Mateer, F. M., and Leinberger, M. H.: Muscular Dystrophy: V. Blood Sugar and Serum Electrolytes Following Insulin and Dextrose, Alone or in Combination, A. M. A. J. Dis. Child. 91: 429-435 (May) 1956.

10. Fergus, E. B.; Nichols, W. R.; Horne, L. M., and Danowski, T. S.: Muscular Dystrophy: VI. Diminished Blood Sugar and Serum Electrolyte

Responses to Epinephrine, A. M. A. J. Dis. Child. 91:436-441 (May) 1956.

11. Albright, E. C.; Larson, F. C., and Deiss, W. P.: Thyroxine Binding Capacity of Serum Alpha Globulin in Hypothyroid, Euthyroid, and Hyperthyroid Subjects, J. Clin. Invest. 34:44-47 (Jan.) 1955.

12. Keitel, H. G., and Sherer, M. G.: Marked Depression of the Plasma Protein-Bound Iodine Concentration in the Absence of Clinical Hypothyroidism During Testosterone Medication, J. Clin. Endocrinol. 17:854-861 (July) 1957.

13. Federman, D. D.; Robbins, J., and Rall, J. E.: Effects of Methyl Testosterone on Thyroid Function, Thyroxine Metabolism, and Thyroxine-Binding Protein, J. Clin. Invest. 37:1024-1030 (July) 1958.

14. Lewis, L. A., and McCullagh, E. P.: Carbohydrate Metabolism of Animals Treated with Methyl Testosterone and Testosterone Propionate, J. Clin. Endocrinol. 2:502-506 (Aug.) 1942.

15. McCullagh, E. P., and Lewis, L. A.: Carbohydrate Metabolism of Patients Treated with Methyl Testosterone: Hypogonadism, J. Clin. Endocrinol. 2:507-510 (Aug.) 1942.

16. Talaat, M.; Habib, Y. A., and Habib, M.: The Effect of Testosterone on the Carbohydrate Metabolism in Normal Subjects, Arch. internat. pharmacodyn. 111:215-226, 1957.

The Effect of Large Doses of Prednisone on Acute Rheumatic Fever

Observations on the Treatment of Seventeen Patients with Carditis with a Two-Year Follow-Up

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The introduction of steroids has presented a new therapeutic approach to the treatment of rheumatic fever. This problem has been the subject of extensive studies over the past few years. The detailed observations made in an effort to evaluate the effect of hormone therapy have resulted in a renewed interest in many aspects of this disease.

In 1955, when a newly synthesized steroid, prednisone, became available, a study was undertaken to test its effectiveness in children with rheumatic fever. The objectives of this study were (1) to determine the relative anti-inflammatory potency of this new steroid in rheumatic fever; (2) to determine what proportion of children with rheumatic carditis treated early in their first attack with large amounts of prednisone for a prolonged period would escape permanent cardiac damage; (3) to determine whether extension of steroid therapy to 14 weeks, in contrast to the conventional 6 weeks, would reduce the incidence of recurrence of symptoms when prednisone was withdrawn, and (4) to determine whether administration of prednisone, in contrast to cortisone, could be tolerated without serious electrolyte imbalance, even when dietary sodium was not restricted and potassium was not added.

This report is concerned with 17 patients with acute carditis who were treated with large doses of prednisone over relatively long periods of time. The observations made on the clinical, metabolic, and toxic effects of the drug are recorded. The number of patients treated is too small to permit any conclusion on the incidence of residual rheumatic heart disease.

Method of Study

Selection of Patients.—The 17 patients with acute rheumatic fever included in the study were treated at one of the following hospitals: Harriet Lane Home, The Johns Hopkins Hospital, Sinai Hospital, and Baltimore City Hospitals. They ranged in age from 5 to 13 years. Six were Negroes. Children with acute rheumatic fever were included if their illness was of less than 30 days' duration and if they presented unequivocal evidence of active carditis. The diagnosis of carditis was based on one or more of the following signs: (1) endocarditis, as manifested by a significant systolic murmur or any diastolic murmur; (2) myocarditis as indicated by tachycardia, poor quality heart sounds, and enlargement of the heart with or without cardiac failure, or (3) pericarditis.

Fourteen of the seventeen patients were in their first attack of rheumatic fever. There was a questionable history of a previous attack in two children and a known prior episode in one. These three patients were known to have clinically normal hearts at the onset of the treated episode. Among the 17 patients none showed evidence of extremely severe carditis. Carditis was graded as mild in 5 and moderately severe in 12 patients. The designation of mild carditis was used for patients who had a blowing systolic murmur of Grade 1-2 (Levine) intensity. In the majority of these children, other

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TABLE 1.—*Pertinent Data*

Case	Age, Yr.	Race	Sex	Duration Prior to Therapy, Days	Severity of Carditis *	Prednisone Therapy		Cardiac Abnormality †		
						Duration, Days	Total Dose, Gm.	End of Therapy	At 1 Yr.	At 2 Yr.
1‡	6	W	M	9	++	108	4.90	? AS	? AS	? AS
2	11½	W	F	7	++	99	4.25	MI	MI	MI
3	10	N	F	2	+	99	3.90	--	--	--
4	10½	N	F	7	++	103	5.07	--	--	--
5	8½	W	F	15	+	95	3.02	? MI	? MI	? MI
6	9	W	M	25	++	96	4.52	--	--	--
7	10	W	M	17	+	95	4.53	--	--	--
8	9½	N	M	26	+	95	4.80	--	--	--
9	13	N	F	2	+	100	4.81	--	--	--
10	7	W	M	4	++	98	4.77	AI	AI	AI
11	6	W	M	21	++	95	4.22	--	--	--
12	6	W	F	30	++	94	4.54	MI	--	--
13	9	W	M	7	++	117	5.10	AI	AI	AI
14‖	5	N	M	4	++	104	3.71	--	--	--
15	7½	W	F	10	++	99	4.08	--	--	--
16	8	W	F	7	++	94	3.66	--	--	--
17	9	N	F	14	++	196	6.82	AI-MI	AI-MI	AI-MI

* + indicates mild; ++, moderate.
† AS, apical systolic murmur; MI, mitral insufficiency; AI, aortic incompetence.
‡ Associated hydronephrosis.
‖ Associated tuberculosis.

manifestations of carditis, such as tachycardia, poor heart sounds, pathological third heart sound, or electrocardiographic abnormalities, were also present. The 12 patients with moderately severe carditis showed one or more of the severe manifestations of carditis: an apical systolic murmur of at least Grade 3 intensity, a diastolic murmur, cardiac enlargement, or evidence of pericarditis. The pertinent data are summarized for each patient in Table 1.

General Measures.—All patients were hospitalized before therapy was begun and were kept on bed rest in the hospital or convalescent home throughout the entire course of treatment. The admission examination included an electrocardiogram and a teleoroentgenogram of the chest, both of which were repeated at intervals thereafter. The sedimentation rate, C-reactive protein determination, and body weight were recorded at weekly intervals. In order to eradicate Group A streptococci, therapeutic doses of penicillin were given during the first 10 days of hospitalization. This was followed by daily prophylactic doses of oral penicillin. All of the children received a regular diet without salt restriction. No additional potassium was given. Serum electrolytes were determined at weekly intervals in the majority of patients.

Throughout the entire study all patients were examined repeatedly by at least two of us (C. F. and M. M.), either in the hospitals or in the convalescent homes, and after discharge from these institutions, the patients were examined at monthly intervals in the follow-up rheumatic fever clinics of the participating hospitals. Penicillin prophylaxis against streptococcal infections was maintained in all patients.

Dosage of Prednisone.—Prednisone* was administered in a dosage of 50 to 75 mg. given divided into four doses each day over a period of nine weeks. This dose was selected as the equivalent of the 200 to 300 mg. of cortisone used in previous studies.[3] In general, the smaller children received the 50 mg. daily dose. After the initial course of nine weeks the drug was then tapered over a period of four to six weeks. The average length of treatment was 14 weeks with the exception of one patient (Case 17) who was treated for 28 weeks and who received a total of 6.8 gm. of prednisone. The total dose in the other 16 children ranged from 3.6 to 5.1 gm. with an average of 4.8 gm. The average dosage schedule was as follows:

Mg/Day	Days, No.
75	28
60	21
50	14
40	7
30	7
20	7
15	7
10	4
5	4
Total 4.8 gm.	14 wk.

* The prednisone used in this study was supplied by the Schering Corporation, Bloomfield, N. J., and by Merck & Co., Inc., Rahway, N. J.

Observations During Therapy

General Anti-Inflammatory Effect.—Fever subsided rapidly in all patients. Indeed, the fall in temperature after the initial dose was so abrupt that in some of the more toxic patients profuse diaphoresis and weakness followed. Consequently later in the study, a child who showed a high fever received a small initial dose, repeated at more frequent intervals, so that the total daily dose was maintained.

Prednisone administration was followed by a satisfactory subsidence of polyarthritis in all patients. The articular symptoms cleared within 12 to 48 hours after the beginning of therapy.

Effect on Acute Cardiac Manifestations. Tachycardia subsided rapidly in all but one patient (Case 17). A bradycardia developed in five children within a few days after onset of therapy. In the only patient (Case 6) with a pericardial friction rub, this sign disappeared at the end of 12 hours of treatment. Abnormalities in the electrocardiogram persisted for a variable length of time. In nine patients in whom a prolongation of the P-R interval was present at the onset of treatment, this finding persisted for 3 to 21 days, with an average duration of 11 days. ST segment and T-wave changes, which occurred in three patients, persisted for 3, 5½, and 8 weeks, respectively.

In four of the five children with mild carditis the apical systolic murmur disappeared within the first two weeks of therapy. In the fifth child the murmur diminished in intensity after six weeks of therapy, but a variable soft systolic murmur remained at the apex. We have hesitated to consider this a functional murmur. None of these five children showed cardiac enlargement at any time.

In the group of 12 children with moderately severe carditis at the onset of therapy, 11 showed evidence of regression of their cardiac findings. One child (Case 17), who developed progressive heart disease while on treatment, will be discussed later in detail. Nine of the eleven patients had moderately loud apical systolic murmurs initially. In each instance the murmur diminished in intensity, and in seven it disappeared completely during therapy. In these seven children the murmur was present for a period varying from 12 to 70 days. The average duration was 30 days. In six children an apical diastolic murmur was present initially and was heard for a period varying between 5 to 18 days. The average duration was nine days. The diastolic murmur disappeared in all instances. Three patients had aortic diastolic murmurs. This murmur remained unchanged in one child. In the second patient the murmur disappeared after 29 days of treatment. In the third patient the aortic diastolic murmur disappeared after 40 days of treatment but reappeared by the 66th day.

In this group of 12 patients with moderately severe carditis, 5 children showed evidence of cardiac enlargement at the onset of treatment. Accurate evaluation of the cardiothoracic ratios during the course of treatment was difficult because of the abdominal distention which occurred secondary to prednisone therapy. By the end of treatment the heart size had returned to normal in each instance. None of the patients were in failure before treatment, and none developed evidence of decompensation during therapy.

One child (Case 17) showed evidence of progressive carditis during therapy. A brief summary of the history follows.

CASE 17.—A 9-year-old Negro girl was admitted to The Johns Hopkins Hospital with her first attack of rheumatic fever, of two weeks' duration. Physical examination revealed arthritis and carditis. There was a Grade 2 apical systolic murmur, slight cardiac enlargement, and prolongation of the P-R interval. Prednisone therapy (75 mg. per day) was begun three days after her admission. Shortly after the onset of therapy a short apical diastolic murmur was heard which became rumbling in quality. The apical diastolic murmur disappeared at the end of the first week of therapy, but the systolic murmur and tachycardia persisted. In the 10th week of therapy, while she received 30 mg. of prednisone per day, a blowing diastolic murmur was first heard at the left sternal border. Prednisone dosage was therefore increased to 40 mg. per day for another three weeks and then slowly

TABLE 2.—*Severity of Carditis and Residual Heart Disease One Year Later Correlated with Duration of Disease Prior to Therapy*

Duration of Symptoms Prior to Therapy, Days	Patients, No.	Severity of Carditis at Onset			
		Mild		Moderate	
		No RHD	RHD	No RHD	RHD
0- 7	8	2	0	3	3
8-14	2	1	0	0	?1
15-21	4	1	?1	1	1
22-30	3	0	0	3	0
Total	17	4	?1	7	4+?1
		5		12	

TABLE 3.—*Side-Effects of Therapy*

Side-Effect	Patients, No.	Time Onset, Wk.	Duration
Moon face	17	1-3	2-7 mo. after therapy
Abdominal fullness	17	½-5	2-7 mo. after therapy
Hirsutism	13	3	Variable, some noticeable 6-8 mo. after therapy
Cutaneous striae	13	5-6	Fading 2-3 mo. after therapy
Hepatomegaly	9	½-4	1-9 wk.
Acne	6	1½-8	2-8 wk., 1 persistent for 8 mo.
Hypertension	3	2-6	3-6 wk.

reduced while full doses of acetylsalicylic acid were given. The total course of prednisone therapy was 28 weeks, and the aggregate dose was 6.8 gm. One week after the cessation of therapy the sedimentation rate became markedly elevated and then declined gradually over a period of eight months. At the end of one year a soft systolic murmur and a loud aortic diastolic murmur were present. During the next six weeks the apical systolic murmur had disappeared, but the aortic diastolic murmur has remained, although it has diminished in intensity. This patient was the only one in the group who showed progression of her cardiac disease while on large doses of steroid for a period of more than four months.

Cardiac Status During the Follow-Up Period

Follow-up studies one year from the beginning of treatment revealed that 11 of the 17 children had normal hearts on clinical examination (Table 2). One of the five patients (Case 5) who had mild carditis at the onset had an apical systolic murmur which varied in intensity and location and was thought to indicate questionable mitral disease. Four of the group of twelve children with moderately severe carditis at the onset had definite rheumatic heart disease: one child had mitral insufficiency (Case 2), two had aortic incompetence (Cases 10 and 13), and one had mitral insufficiency and aortic incompetence (Case 17). Questionable heart disease as evidenced by a slight systolic murmur in the aortic area was present in another patient (Case 1).

During the second year of follow-up further regression of cardiac findings occurred. The murmur of mitral insufficiency diminished markedly in Case 2 and disappeared in Case 17. The murmur of aortic incompetence diminished in intensity in Cases 10 and 17. Thus, at the end of two years, of the total group of 17 children, 4 patients showed definite rheumatic heart disease and in 2 patients questionable heart disease was present. None of the children had cardiac enlargement.

Fig. 1.—Marked striae over abdomen and thighs of a 7-year-old girl (Case 15) at the end of 99 days of prednisone treatment, total dose 4.08 gm.

Side-Effects

Side-effects of therapy were noted in all patients, and these are listed in Table 3 according to frequency, time of onset during therapy, and duration. There was no instance in which therapy had to be discontinued because of dangerous side-effects and only one instance in which reduction of dosage was necessary (Case 1).

Moonface, abdominal fullness, and *hirsutism* were striking in all patients. Severe *cutaneous striae* (Fig. 1) caused considerable emotional distress, especially in some of the girls.

Hypertension represented the most serious side-effect. It was marked in three patients and mild in two. In one child (Case 1) a convulsion occurred during a hypertensive episode on the 27th day of therapy. In another patient (Case 2) the blood pressure was consistently elevated during the fourth to eighth weeks of therapy, with the highest reading of 160/110. During the 8th-10th weeks only occasional elevated pressures (above 120/80) were recorded, and thereafter the blood pressure was normal. This girl was asymptomatic throughout the period of hypertension. The third patient (Case 5) showed a consistently elevated blood pressure during the sixth to ninth weeks of therapy, with the highest reading of 140/110. There were no associated symptoms.

Two other patients (Cases 7 and 8) had high normal pressures recorded during the second to sixth weeks, and the fourth to eighth weeks, respectively, with occasional values as high as 150/80 and 144/108, but hypertension was not sustained.

Our concern about the occurrence of hypertension was great because we had seen one instance in which severe hypertension developed during prednisone therapy and persisted for several weeks after treatment was interrupted.†

Hepatomegaly was noted during therapy in 9 of the 17 patients. None of these children had evidence of heart failure. An accurate evaluation of the size of the liver was rendered difficult by the abdominal distention which occurred in all patients during treatment. Enlargement of the liver was fairly marked and prolonged in only one child (Case 1). In some children

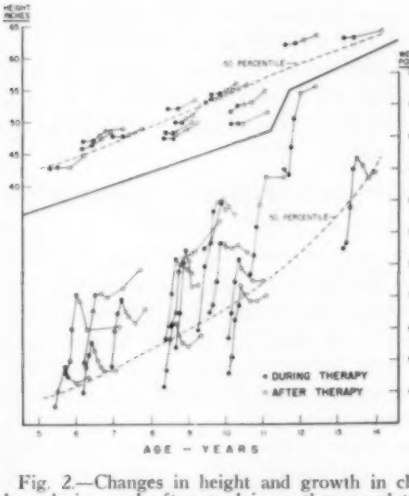

Fig. 2.—Changes in height and growth in children during and after prednisone therapy plotted in relation to a percentile curve (Children's Medical Center, Boston, Anthropometric Chart).

† A 7-year-old boy received the same course of therapy as outlined above. He is not included in this series because treatment was not commenced until the seventh week of his initial attack of rheumatic fever. In this instance alarming hypertension was observed during therapy. The blood pressure recorded before therapy was 125/80, and it was 135/90 on two occasions. He received 75 mg. of prednisone per day, and by the third week the diastolic pressure was consistently over 100 mm. Hg. Prednisone dosage was lowered to 60 mg. on the 17th day and to 50 mg. on the 22d day. In spite of this the blood pressure remained between 140/96 and 180/140. Steroid dosages was then rapidly tapered off and discontinued on the 41st day, while acetylsalicylic acid was substituted. In spite of this change in regimen the blood pressure remained at the previous elevated levels. Reserpine was given in a dosage of 0.02 mg. per kilogram without any appreciable effect over the next four weeks. He also received sedation. During this period the lowest blood pressure recorded was 130/80 on one occasion. The first normal reading of 120/74 was obtained seven weeks after steroid therapy was discontinued. Investigation of the urinary tract demonstrated no abnormality. During the two-year follow-up period this child has shown a consistently normal blood pressure. It is therefore reasonable to attribute the hypertension to the steroid therapy.

hepatomegaly was associated with slight tenderness in the right upper quadrant for a few days.

Acne occurred in six patients. It was noted as early as the 10th day of therapy in an adolescent girl (Case 2). In this instance, the acneiform rash persisted for many months thereafter. In the other five children the acne appeared between the fourth and eighth weeks of therapy and lasted for two to eight weeks.

Changes in weight gain and growth were noted during therapy (Fig. 2). Every patient showed an excessively rapid increase in weight during steroid administration, and this was followed by a slow return to normal weight after discontinuation of treatment. Changes in growth were less striking but, we believe, significant. Most patients failed to grow during the treatment period, but growth was resumed at a normal rate as soon as the drug was stopped. Thus at the end of one year, there was no appreciable delay in growth but most patients were still overweight.

Serum electrolytes were determined in 14 of the patients at the onset of treatment and at frequent intervals thereafter. All of these children were on a regular hospital diet without restriction of salt or addition of potassium. After the subsidence of the acute manifestations, there was usually a marked increase in appetite which was satisfied by liberal additions to the regular diet. The exact daily intake of salt and potassium was not known.

The results of the serum determinations for bicarbonate, sodium, and potassium expressed in milliequivalents per liter is shown in Figure 3. Three children had an elevation in serum bicarbonate of between 27 and 30 mEq. per liter prior to the administration of steroids. During the course of prednisone treatment, three-fourths of the bicarbonate determinations were in the range of 27 to 33 mEq. per liter and 50% of these were 30 mEq. per liter or greater. These results indicate that a rise in serum bicarbonate occurs frequently when large doses of prednisone are used. None of these patients showed any signs of alkalosis.

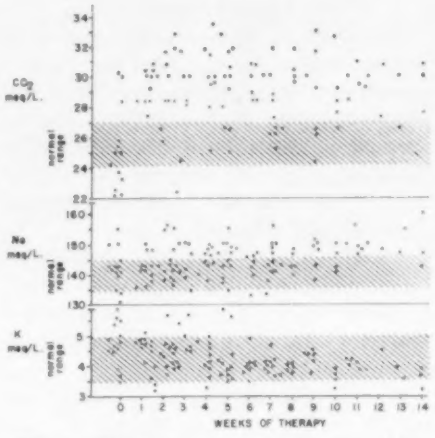

Fig. 3.—Distribution of serum Na, K, and CO_2 determinations in 14 patients before and during prednisone therapy.

The alterations in serum sodium were not as striking as those recorded for bicarbonate. In general, there tended to be some elevation in serum sodium but this finding was not a consistent one. There was no evidence of edema in any of the children.

The serum potassium showed an over-all downward drift as therapy progressed, but in almost all of the patients the potassium remained above 3.5 mEq. per liter. Three children did have a level of between 3 and 3.5 mEq. per liter on single occasions. In this connection, it is of interest to note that the rise in serum bicarbonate was not accompanied by a significant fall in serum potassium.

Recurrence of Rheumatic Manifestations After Therapy

In spite of the relatively long period of time during which suppressive therapy was administered, all but two children showed a return of abnormal clinical or laboratory findings during or after reduction of the prednisone dosage. Recurrence of rheumatic manifestations was not only frequent, but also often severe and persisted for a long time afterward. The most important manifestations plotted in relation to the decrease in prednisone dosage are shown

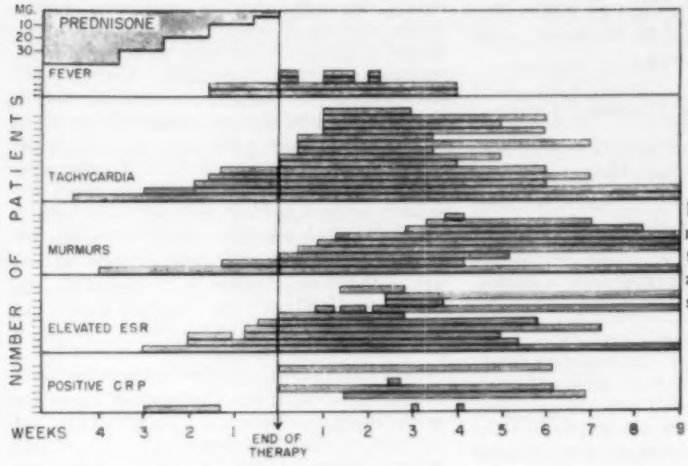

Fig. 4.—Clinical and laboratory recurrence of rheumatic manifestations toward the end of and after cessation of prednisone therapy.

in Figure 4. Table 4 shows the coexistence of the various manifestations.

The following discussion of the problem concerns only 16 of the 17 patients, as one child (Case 17) received full doses of acetylsalicylic acid when steroid therapy was discontinued after a prolonged course.

Of these 16 patients, recurrent rheumatic manifestations appeared during the period of decreasing prednisone dosage in 7 and after cessation of therapy in 7 others. In all instances, more than one abnormal finding was noted.

Tachycardia and an elevated sedimentation rate were the commonest findings, but fever, arthralgia, abdominal pain, erythema, and return of C-reactive protein were also noted.

The most disturbing occurrence was the return of abnormal cardiac findings in 9 of the 16 children. In two patients the apical systolic murmur became louder. In six patients the apical systolic murmur, which had previously disappeared, returned. Two of these six patients developed systolic murmurs at the aortic area not present during the initial episode. All of these systolic murmurs disappeared within four to nine weeks. In one patient, an aortic diastolic murmur which had disappeared by the 40th day of therapy (on 50 mg. per day) became audible again on the 66th day (on 30 mg. per day).

None of these patients in whom a recurrence of rheumatic manifestations developed received a second course of treatment. The

TABLE 4.—*Prednisone Therapy—Manifestations During and After Reduction of Dosage* *

	Total No.	Fever	Tachycardia	Murmurs	Arthralgia	Abd. Pain	Rash	ESR	C-R Protein
Fever	4		4	1	2	--	1	3	3
Tachycardia	14	4		9	2	1	1	12	7
Murmurs	9	1	9		1	1	--	8	4
Arthralgia	2	2	2	1		--	--	2	2
Abd. pain	1	--	1	1	--		--	1	--
Rash	1	1	1	--	--	--		--	--
ESR	12	3	12	8	2	1	--		7
C-R protein	7	3	7	4	2	--	--	7	

* Total of 16 patients; total with rebound, 14. Patient 17, who showed progressive diseases during therapy and whose treatment after five weeks was changed to acetylsalicylic acid, is not included in this table. Each manifestation of rheumatic activity which recurred after the prednisone dosage was decreased is listed both horizontally and vertically to show the coexistence of the abnormal findings, e. g., nine patients had a recurrence of murmurs, of these one had a fever; all nine had tachycardia.

time required for subsidence of signs and symptoms varied from 2 to 16 weeks, with an average time of 8 weeks.

Intercurrent Illnesses

Coexistent disease presented additional problems in two patients. In one child a congenital ureteropelvic obstruction produced an acute illness during the second week of steroid therapy. Another child developed acute primary tuberculosis during the rheumatic episode. A brief summary of these patients follows:

CASE 1 *(Hydronephrosis).*—A 6-year-old white boy was admitted to the Sinai Hospital with acute rheumatic carditis. His initial response to a daily dose of 75 mg. of prednisone was satisfactory. On the 11th hospital day he developed a temperature of 102 F and severe generalized pain, which gradually became localized to the right costovertebral angle. The blood pressure was 130/100; the white blood cell count rose to 22,000; the urine was normal, and the blood urea was 71 mg. %. An intravenous pyelogram showed an enlarged right kidney with evidence of ureteropelvic obstruction. Prednisone was continued, with the exception of a 12-hour period when 100 mg. of intravenous hydrocortisone was substituted because of vomiting. The pain subsided by the 15th hospital day without any additional therapy. After the above episode, the blood pressure returned to more normal levels until the 27th day, when it rose to 136/100. The following day he was found in coma, and shortly thereafter he had a generalized clonic convulsion. His blood pressure at this time was 158/116. Rectal paraldehyde was given. He remained semicomatose for several hours. During the 24-hour period after the onset of the coma and convulsions, he was given 100 mg. of intravenous hydrocortisone. By the 29th hospital day, he seemed entirely normal again, and prednisone was again administered in a daily dose of 50 mg. His blood pressure ranged between 130/70 and 140/92 over the next two weeks and then returned to normal levels. The episode was considered as an attack of hypertensive encephalopathy as the result of steroid therapy. The rise in blood pressure may have been enhanced by the underlying kidney disease. Two years later surgical reconstruction of the ureteropelvic junction was performed without incident. It is of interest to note that the large dose of steroid did not mask the abdominal pain nor the localizing muscle spasm in the region of the right kidney.

CASE 14 *(Tuberculosis).*—Acute primary pulmonary tuberculosis occurred coincident with rheumatic fever in a 5-year-old Negro boy. Admission chest film showed no evidence of pulmonary disease. During the sixth week of prednisone therapy (while receiving 50 mg. per day) the patient developed a low-grade afternoon elevation of temperature and slight tachycardia. Early in the seventh week the temperature rose to 40.4 C (104.72 F) and he appeared acutely ill. An x-ray of the chest revealed a left upper lobe infiltration suggestive of primary tuberculosis. On the same day that the pulmonary infiltration was noted, the patient's infant sister was admitted to the hospital with tuberculous meningitis. The tuberculin test was positive. Streptomycin and isoniazid therapy was instituted, and the dose of prednisone was decreased to 25 mg. per day. Steroid dosage was then lowered by 5 mg. every two weeks for a period of two more months.

The child continued to show spikes of temperature up to 40.5 C (104.9 F) for seven days. The sedimentation rate became markedly elevated and remained so until four weeks after therapy was stopped. Return of serum C-reactive protein was also noted in association with the acute tuberculosis but disappeared within two weeks. The pulmonary lesion showed radiological evidence of regression within one month of antituberculosis therapy and cleared completely during the next four months. After discontinuation of steroid therapy a return of active rheumatic carditis was noted, as manifested by the development of a systolic murmur in the aortic area. This manifestation subsided and the heart appeared clinically normal three months after therapy. It was the opinion of the attending chest physician that the character and course of the acute primary tuberculosis was not influenced by steroid therapy, nor was any suppression of the systemic manifestations of tuberculosis apparent.

Comment

This study was designed soon after the observation was made that prednisone, a newly synthesized 11,17-oxygenated steroid, possessed anti-inflammatory potency greater than that of cortisone or hydrocortisone and was free of the hazards of serious electrolyte imbalance and water retention.[2] Since the retention of sodium and water were troublesome side-effects commonly encountered when cortisone was used in patients with rheumatic carditis, the special advantage of using prednisone in such patients became self-evident. Furthermore, it seemed not unlikely that prednisone would be but the first of a series of synthetic cortisone analogues. What specific advantage (or hazard) each of these new compounds could offer in the various

diseases effectively suppressed by steroid administration could only be determined by careful clinical trial.

Admittedly, it would have been desirable to include in such a trial randomly allocated, alternate controls treated with salicylates. This would, however, have required a much larger number of patients with acute rheumatic carditis. It seemed desirable to obtain clinical experience with this new steroid before larger scale controlled studies were undertaken.

The results of this study indicate that prednisone is three to four times more potent on a weight basis than cortisone as an anti-inflammatory and antirheumatic agent in acute rheumatic fever. There was, however, no evidence that the development of residual rheumatic heart disease was prevented in all patients. At the end of two years of observation 4 of the 17 children had unequivocal organic heart disease. In a series of 29 children similarly selected and treated for 2 to 10 months with a comparable dosage of cortisone, Markowitz and Kuttner[3] found that about the same proportion developed rheumatic heart disease. Although the samples are not large, the results obtained after administration of prednisone and cortisone appear to be comparable.

We were impressed with the high incidence (87%) of recurrence of rheumatic manifestations when prednisone was reduced in dosage or discontinued. For example, 14 of 16 patients had recurrence of tachycardia, murmurs reappeared or became louder in 9 patients, and the erythrocyte sedimentation rate rose in 12. This suggests that in spite of prolonged therapy rheumatic activity was not arrested. Since the untreated acute attack of carditis is not likely to exceed 12 weeks, it is reasonable to conclude that recurrence of rheumatic activity was not due to premature discontinuance of the steroid. The cause of the recurrence which follows steroid withdrawal remains obscure. More recent experience with a different dosage regimen suggests that the high dosage and the rapid tapering used in this study may have contributed to the frequent reappearance of rheumatic manifestations.

Although dietary sodium was taken in liberal and unrestricted amounts and potassium was not supplemented, it is impressive that neither edema nor clinical or laboratory signs of hypokalemia developed in these children. However, a significant rise in serum bicarbonate did occur in the majority of children during prednisone therapy. This elevation of serum bicarbonate occurred without any significant change in the serum potassium. These data are of particular interest in view of the recent experimental studies carried out by Grollman and Gamble.[4] These workers found that a metabolic alkalosis occurred in the absence of a demonstrable cellular potassium deficit in animals treated with steroids. The mechanism by which steroids produce this disturbance is not known.

While prednisone is a much less hazardous drug than cortisone or hydrocortisone from the point of view of electrolyte disturbances, other undesirable side-effects were encountered. Every child manifested one or more signs of hypercorticalism. Some of these signs, particularly cutaneous striae, appeared more commonly and to a greater degree than previously seen in children treated with comparable doses of cortisone. The most serious side-effect was hypertension, which in one patient was life-threatening. Other adverse effects, such as gastrointestinal hemorrhage, perforation of peptic ulcer, polyarteritis nodosa, and fractured vertebrae, encountered in adult patients with rheumatoid arthritis were conspicuously absent in this series. Likewise the erythema nodosa-like lesions described by Good et al.[5] were not noted. While all of the toxic reactions which we observed disappeared completely, the need for careful and frequent observations in patients treated with prednisone must be emphasized.

Summary

Seventeen children with clinical evidence of acute rheumatic carditis of less than one month's duration were treated with large

doses of prednisone for an average period of 14 weeks.

Prednisone produced a satisfactory response in fever and joint manifestations in all patients. In general, the anti-inflammatory and antirheumatic effects of prednisone in doses of 50 to 75 mg. per day were comparable to those noted in previous studies with 200 to 300 mg. per day of cortisone.

The use of a relatively long course of treatment did not prevent a return of rheumatic manifestations when prednisone was terminated. Recurrences occurred in 87% of the patients but subsided without treatment in all instances.

All of the children developed marked signs of hypercorticalism. None of the patients developed edema or hypokalemia on a normal diet without the addition of potassium. Hypertension was the most serious toxic effect encountered and was the cause of a convulsion in one patient.

At the end of a two-year follow-up period, 4 of 17 patients had evidence of rheumatic heart disease. Two additional patients had questionable heart disease. While no conclusions can be drawn from this small uncontrolled study of the efficacy of prednisone in reducing the incidence of heart disease, these results indicate that the use of large doses of this steroid over a prolonged period in children early in their attack does not prevent cardiac sequelae in all patients.

Dr. Harold Harrison, of the Baltimore City Hospital, gave permission for rheumatic patients to be followed on his service.

Children's Hospital (29).

REFERENCES

1. Greenman, L.; Weigand, F. A., and Danowski, T. S.: Cortisone Therapy in Initial Attacks of Rheumatic Carditis, Ann. Rheumat. Dis. 12:342, 1953.

2. Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis: Antirheumatic Potency, Metabolic Effect, and Hormonal Properties, J. A. M. A. 157:311, 1955.

3. Markowitz, M., and Kuttner, A. G.: The Effect of Intensive and Prolonged Therapy with Cortisone and Hydrocortisone in First Attacks of Rheumatic Carditis. Pediatrics 16:325, 1955.

4. Grollman, A. P., and Gamble, J. L., Jr.: Metabolic Alkalosis: A Specific Effect of Adrenocortical Hormones, A. M. A. J. Dis. Child. 96:494, 1958.

5. Good, R. A.; Vernier, R. L., and Smith, R. T.: Serious Untoward Reactions to Therapy with Cortisone and Adrenocorticotropin in Pediatric Practice: Part I, Pediatrics 19:95, 1957.

Parenteral Trypsin in Trauma

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Widespread interest in parenterally administered proteolytic enzymes in the treatment of trauma is apparent from an examination of the recent literature.[1-5] Many enzymes and various routes of administration have been used. Most authors agree that the enzymes are materially beneficial, but their enthusiasm seems to be based on "clinical impressions," clinical observations or subjective improvement. For example, Lichtman [6] administered trypsin parenterally to 350 athletes who had sustained bruises, with "excellent" results in 66% of those treated. To either confirm or disprove the reports in the literature, an entirely objective and controlled approach to the problem was essential. Washing machine wringer injuries of the arm in children are common in this area and seemed to present possibilities for a uniformly controlled study, because edema of the arm could be measured accurately, and tenderness could be evaluated objectively.

In this series lyophilized trypsin, in 5% aqueous gelatin solution (Parenzyme Aqueous),* was used intramuscularly.

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* Parenzyme Aqueous was furnished by Mr. William M. Swain of The National Drug Company, Philadelphia.

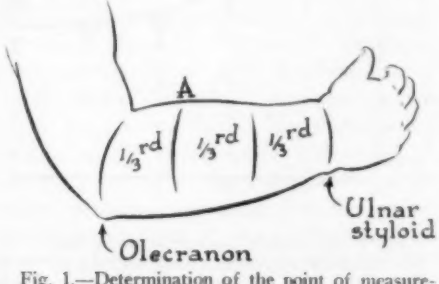

Fig. 1.—Determination of the point of measurement of the forearm.

Methods

For a period of two years all children under 12 years of age who presented themselves with "wringer injuries" of the upper extremity were admitted to the hospital and treated as described below.

A complete history, physical examination, blood count, urinalysis, and x-ray of the injured arm were obtained upon admission. The length of the forearm was measured from the ulnar styloid process to the tip of the olecranon process and

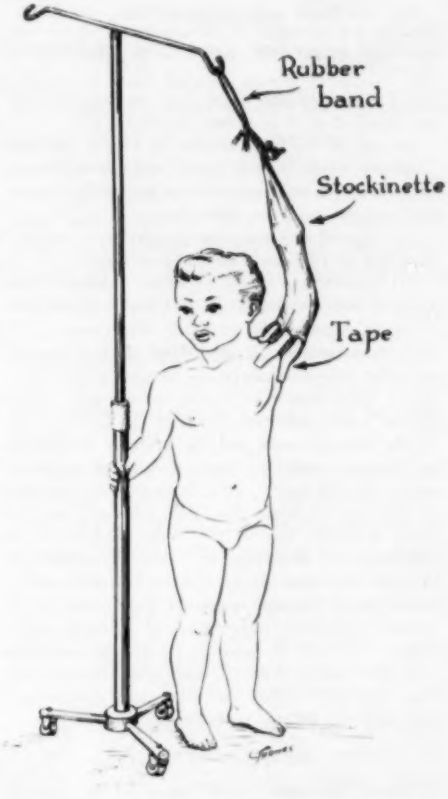

Fig. 2.—The method of elevation used in this study.

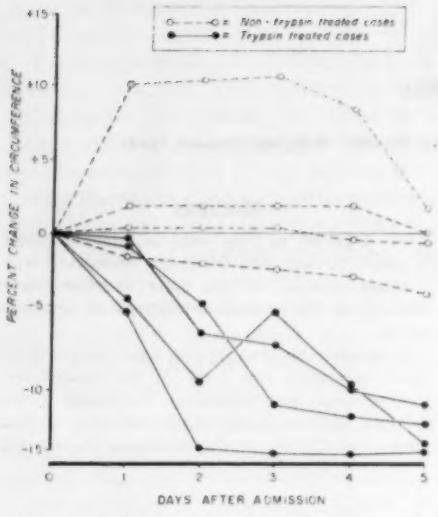

Fig. 3.—Eight typical cases from the study, showing the variation of circumference of the arm expressed in per-cent change from the admitting circumference.

this was divided into three equal lengths. A point was marked at *A* as shown in Figure 1.

Because of the large amount of muscle and subcutaneous tissue in this region, the circumference of both arms was measured at this point on admission and every day thereafter.

The injured arm was then elevated by a method described in 1957 and illustrated in Figure 2.

No constricting elastic or other bandages were applied, and the joints of the upper extremities were not immobilized.

Every patient was given 300,000 units of aqueous penicillin intramuscularly on admission and twice daily. Appropriate antitetanus therapy was administered when indicated.

The circumference and the presence or absence of forearm tenderness were recorded on admission and every 24 hours. (To determine the presence or absence of tenderness, firm pressure was applied at point "A" on the volar surface of the forearm, and "flinching" or attempt at withdrawal of the arm was recorded as a positive sign of tenderness.) In addition to the above, half of the patients received intramuscular (gluteal) injections of 5 mg. of aqueous trypsin on admission and twice daily. Patients with even hospital numbers received trypsin, and those with odd hospital numbers did not received trypsin.

Selection of Cases

All of the cases treated could not be included; therefore, certain criteria for selection of cases were established.

1. The age of the patient was between 1 year and 12 years.
2. The injury was less than six hours old when treatment was instituted.
3. No lacerations or avulsions of the skin were present.
4. No fracture of the upper extremity was present.
5. The patient was treated and examined for at least five days in the hospital.
6. No other diseases were present.

Results

Twenty trypsin-treated cases and twenty nontrypsin cases met the criteria established for this study.

The circumferences of the arms of 100 uninjured children were measured, and in any given child the size of the two arms varied from 1% to 10%. The dominant arm was not consistently larger than the other arm. After examination of Figures 3 and 4, it is obvious that the normal size of the arm is not necessary for an evaluation of the action of trypsin. Therefore, this method of comparison was discarded,

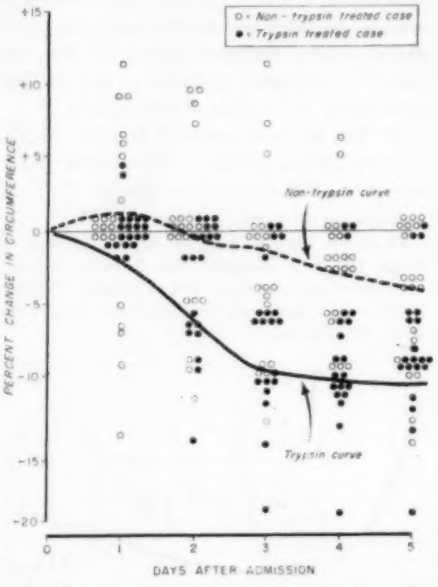

Fig. 4.—A scattergram indicating the daily variation for patients in both groups and the curves of daily variation for each of the two groups (trypsin-treated and nontrypsin-treated).

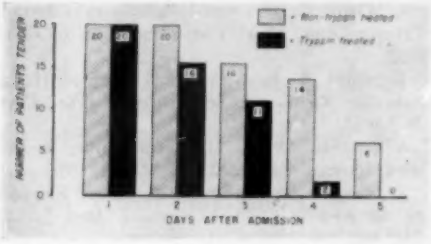

Fig. 5.—The number of patients in each group showing tenderness (objective) on each day following admission.

and the day-to-day variation of the circumference of the injured arm was compared with its own circumference on admission.

Figure 3 shows the circumference of the arm upon admission and each day thereafter in four typical cases each of trypsin and nontrypsin treated cases.

Figure 4 is a scattergraph of all cases with curves drawn through the daily average variation of each group.

Figure 5 shows the number of patients in each group having objective tenderness upon admission and each day thereafter.

Comment

There was seldom an increase in the circumference (edema) of the arm after treatment with trypsin was instituted, and when such an increase did occur it was present only on the first day. In those patients who did not receive trypsin about 50% had an increase in circumference of the arm after admission (some as great as 12%), and this increase remained for as long as five days.

The mechanisms by which trypsin exerts its effect have been postulated by several authors. Martin [8] believes that trypsin acts by direct transfer to the site of inflammation and acts there as a depolymerase to break down the barrier materials which block transfer of fluids. Recent work by Bogner et al.[9] lends some confirmation to Martin's theory, as there was an apparent concentration of radioactivity at the site of inflammation when I^{131}-tagged trypsin was given subcutaneously at a distant site. Innerfield et al.[10] feel that trypsin activates an enzyme in plasma, probably plasminogen, which acts at the inflammatory site in a nonspecific manner. Moser,[3] on the other hand, believes that trypsin provokes an elevation of serum antiproteases which antagonize the proteases that Menkin [11] reported to be present locally at the site of inflammation. These proteases are said by Spector [12] to liberate the polypeptides found so commonly in inflamed areas.

Whatever the mechanism, trypsin appears to mobilize the inflammatory edema fluid. The early relief of pain found in this study (Fig. 5) is probably due to the relief of local pressure of edema fluid at the site of injury. Moss [13] has shown that this early relief of pressure and pain lends itself to better wound healing.

Precautions

An unexplained transient leukopenia was noted in one patient given trypsin. The leukopenia subsided about four days after trypsin treatment was discontinued.

Two patients (not included in this series) were admitted after nonfluctuant hematomas had formed. They were treated with trypsin, and after 48 hours the hematomas developed fluctuant centers. About 72 hours after unsuccessful attempts to aspirate these hematomas the centers sloughed. This delayed healing, and we now believe that trypsin treatment should be delayed until hematomas are fluctuant and can be aspirated.

Several of the older children complained of severe transient pain at the injection site. This was found to be due to injection of the solution into the subcutaneous tissue rather than into the muscle. The solution must be injected deep intramuscularly if pain at the injection site is to be avoided.

Conclusions

The results of this study indicate that trypsin given parenterally is beneficial in the treatment of soft-tissue edema. This beneficial effect apparently results from the reduction of edema fluid brought about by

the action of trypsin. Certainly this study confirms the belief that tenderness, both subjective and objective, is promptly relieved by parenteral trypsin.

The parenteral administration of trypsin is safe and effective in children.

Summary

The results of and conclusions from a controlled study of 40 children with "wringer injuries" of the arm is presented. Twenty were treated with parenteral trypsin and twenty were not.

Texas Medical Center (25) (Dr. Glass).

REFERENCES

1. Hopen, J. M., and Campagna, F. N.: Use of Intramuscular Trypsin, in Traumatic, Inflammatory, and Hemorrhagic Ocular Disturbances, Am. J. Ophth. 40:209-214, 1955.

2. Golden, H. T.: Effective Treatment for Traumatic and Inflamed Lesions Using Trypsin, Clin. Med. 2:583, 1955.

3. Moser, J. M.: Intramuscular Injection of Trypsin, New England J. Med. 256:258-263; 303-309, 1957.

4. Martin, G. J.: Anti-Inflammatory Effect of Trypsin, Ann. New York Acad. Sc. 68:70-88, 1957.

5. Silbert, N. E.: Enzyme Therapy by Intramuscular Route in Chest Diseases, Dis. Chest 29:520-532, 1956.

6. Lichtman, A. L.: Traumatic Injury in Athletes, Internat. Rec. Med. 170:322-326, 1957.

7. Glass, T. G.: A Simple Method of Elevation of the Arm in Children, Texas J. Med. 53:530-532, 1957.

8. Martin, G. J.: Trypsin, the Pharmacology of the Drug, Exper. Med. & Surg. 13:156-171, 1955.

9. Bogner, R. L.; Edelman, A., and Martin, G. J.: In Vivo Observations with Radioactive Trypsin, Arch. internat. pharmacodyn., to be published.

10. Innerfield, I.; Angrist, A., and Schwarz, A.: Parenteral Administration of Trypsin, J. A. M. A., 152:597-605, 1953.

11. Menkin, V.: Dynamics of Inflammation, New York, The Macmillan Company, 1950.

12. Spector, W. G.: The Role of Some Higher Peptides in Inflammation, J. Path. & Bact. 63:93-110, 1951.

13. Moss, J. N.; Brendel, R.; Simon, H.; Beiler, J. M., and Martin, G. J.: Effect of Trypsin on Wound Healing, Arch. internat. pharmacodyn. 60:375-379, 1957.

Bilateral Dwarfed Kidneys

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Small kidneys may be due to faulty development, as in hypoplasia and aplasia, or the cause may be atrophy secondary to disease in normally developed kidneys. In aplasia, specific renal structures are absent. In hypoplasia renal structures are found but in smaller numbers than usual. While aplasia is incompatible with life for more than a brief duration, hypoplasia may occur in different degrees of severity and thus support life for various periods of time.

Atrophy of the kidneys is most often due to pyelonephritis or glomerulonephritis. Frequently, atrophy occurs in hypoplastic kidneys, and it may be exceedingly difficult to decide which is the most important factor in ultimately determining the size of the kidneys.

The following case presents this problem along with some marked changes due to chronic renal insufficiency:

A 10-year-old boy was seen because of shortness of stature. He was 48 in. tall and weighed 51 lb. as compared with 55.2 in. and 71 lb. for the 50th percentile at his age. The parents had noted that he was smaller than his siblings at the age of 2 years, and this difference became gradually more marked. He had been a bed-wetter until the age of 8. At the age of 7, albuminuria was noted by the family physician. At this time there was frequent urination and possibly polydipsia. He was seen in a Crippled Children's Field Clinic at the age of 9 and again six months later. A brownish pigmentation of the skin was noted. Physical examination was otherwise negative. The urine contained no albumin, sugar, or erythrocytes. An occasional leukocyte was seen. The specific gravity of the urine was 1.008. He weighed 44½ lb. and was 45¾ in. tall at the age of 9.

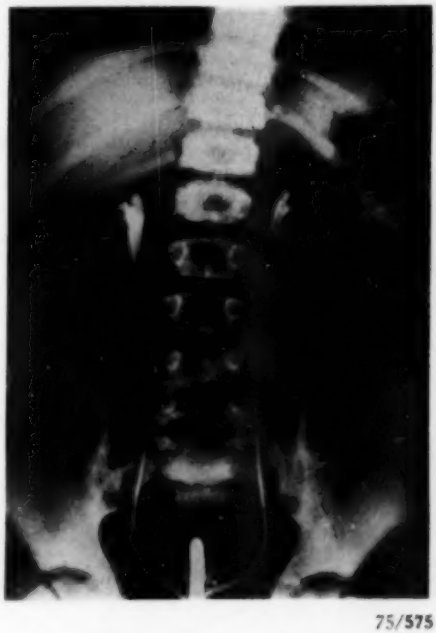
The patient was born at term after an uneventful pregnancy and delivery. An extra phalanx was attached to the distal phalanx of the right thumb, and there was ulnar deviation of the corresponding left phalanx. A nonspecific deformity of both feet was noted. The extra phalanx was later removed and the feet corrected in casts.

The birth weight was 6 lb. 10 oz., and development during infancy was apparently normal. At one year he weighed 18 lb. He was bowel-trained at 2 years. He had chickenpox and measles at the age of 7, but no episode of febrile illness followed by urinary symptoms or swelling could be elicited.

The family history was noncontributory.

Physical examination revealed a well-proportioned, but small, boy in no apparent distress. He had somewhat Negroid features and brownish-yellowish pigmentation of the skin, most marked on the extremities and in the axillae. There was ulnar deviation of the distal phalanx of the left thumb, and he was markedly flat-footed and slightly bowlegged. The blood pressure was 115/85. Examination was otherwise negative. Both testes were in the scrotum.

Fig. 1.—Retrograde pyelogram demonstrating dwarfed kidneys. Each kidney has only three calyces.



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Pediatrician (Dr. Slungaard) and Pathologist (Dr. Jaeck), Gundersen Clinic and LaCrosse Lutheran Hospital.

Variation in Serum Electrolytes and BUN

Date	BUN, mEq/L.	CO_2, Mg. %	K, Mg. %	Na, Mg. %	Cl, Mg. %	Ca, Mg. %	P, Mg. %	Miscellaneous
10/30	140	16	5.4	144	105	9.5	5.8	Serum alb., 6.6 gm.; serum glob., 1.8 gm.; alk. phtse., 17 K-A. units
2/25	130	9	7.4	142	106	10.0	6.9	Urine, 3+ albumin
3/26	208	18	6.0	133	81	9.9	2.8	Serum alb., 3.2 gm.; serum glob., 1.1 gm.

Urinalysis showed 2+ albumin, 8-10 erythrocytes, and 2 leukocytes per high-powered field. The specific gravity was 1.010 and the pH 7.4. Daily urinalyses during the next 14 days showed the specific gravity to vary between 1.008 and 1.010. A concentration test did not bring the specific gravity above 1.010. Maximal dilution was to 1.002. The pH varied from 6.5 to 7.4. Cultures of the urine were negative on two occasions. The blood urea nitrogen (BUN) was 140 mg. %.

Cystoscopy and retrograde pyelography showed the kidneys to be extremely small and the renal pelves narrow and elongated. Only three calyces were seen on each side (Fig. 1).

Daily recordings of the blood pressure showed it to vary between 100 to 136 systolic and 78 to 92 diastolic. The optic fundi were normal.

Further studies were carried out to evaluate secondary changes. Serum CO_2 was 16 mEq. per liter; chlorides, 105; sodium, 144, and potassium, 5.4 mEq. per liter. Serum calcium was 9.5 mg. % and phosphorus 5.8 mg. %. Total serum protein was 6.6 gm. %, with 4.8 gm. % albumin and 1.8 gm. % globulin. Free cholesterol in the serum was 95 mg. % and cholesterol esters 230 mg. %. Fractionation by electrophoresis showed the phospholipid content to be increased to 14 mg. %.

Roentgenograms of the wrists and ribs showed irregular calcification and flaring at the epiphysis (Fig. 2). The bones of the skull, pelvis, and upper extremities showed coarsened trabeculation, and there was delayed bone maturation. The sella turcica was enlarged, and the paranasal sinuses were underdeveloped. Roentgenograms of the chest showed cardiomegaly with normal lungs. Electrocardiograms revealed left ventricular hypertrophy.

The leukocytes in the peripheral blood numbered 5,600. There were 7% monocytes, but the differential count was otherwise normal. The hemoglobin was 6.5 gm. % and the hematocrit 20%. The mean corpuscular volume was 102 cu. μ and the mean corpuscular hemoglobin concentration 32.5%. The reticulocytes numbered from 0.9% to 2%. Fragility of the erythrocytes was slightly increased. A test for sickling was negative.

A smear of the peripheral blood revealed normochromasia and poikilocytosis, but no anisocytosis. The leukocytes showed no morphological abnormalities. The number of platelets appeared normal.

By electrophoretic and alkaline denaturation tests, the hemoglobin was found to be of the adult type. No fetal hemoglobin was present.

A biopsy of the left iliac crest was done after unsuccessful attempts at aspirating bone marrow from the sternum. On examining smears of the bone marrow, depression of the erythroid and myeloid line was found. The erythroid-myeloid layer was 1% and the fat layer 0% of the bone marrow hematocrit. There were 10.6% developing erythrocytes, 41.9% neutrophils and precursors, and 44.6% nonhematopoietic cells, chiefly lymphocytes and histiocytes. The granulocytes showed normal maturation and were somewhat less depressed than the developing erythrocytes. The megakaryocytes appeared normal in number with normal thrombocytogenesis. Many phagocytic cells were seen. Several were filled with lipoid material, so-called "foam cells." Hemosiderin was also found in histiocytes, sometimes along with lipoid material. Several osteoblasts and osteoclasts were present in some smears of the marrow. No tumor or L. E. cells were seen.

Sections of the bone marrow revealed generalized hypoplasia of the hematopoietic elements and rather extensive myelofibrosis. The fibrous tissue appeared

Fig. 2.—The distal metaphysis of the radius and ulna show delayed and irregular ossification of the epiphysial cartilage and slight widening of the osteoid seam. The trabecular pattern of the radius, ulna, metacarpals, and phalanges is coarser than normal. The bone age is about 5 years.

to be young and proliferative. Aggregates of "foam cells" and scattered deposits of hemosiderin pigment could be seen in the proliferating fibrous tissue. Cholesterol crystals were also seen. No granulomata were observed.

A Thorn test showed normal response, and the 17-ketosteroids in the urine were 2.1 mg. in 24 hours. Fasting blood sugar was 115 mg. %. Serum bilirubin was 0.0 direct and 0.2 mg. % total. Thymol turbidity was two units. The basal metabolic rate was —5%, and the radioactive-iodine uptake was 43% in 24 hours.

The patient was closely followed during the next five months until he died. Three blood transfusions were given to keep the hemoglobin around 8 gm. The urine continued to show 2+ albumin with only occasional leukocytes and erythrocytes. The Sulkowitch reaction in the urine was 1+ to 2+. Excretion of amino acids in the urine was within normal limits.

After three months the blood pressure had risen to 150/120 and the BUN to about 200 mg. %. Two episodes of convulsions occurred, which were controlled by amobarbital (Amytal) sodium. Lumbar puncture revealed a spinal fluid pressure of 410 mm. of water. There were 3-4 leukocytes per cubic millimeter, and the content of sugar and chloride was normal. The protein content was 62 mg. %. Smears and culture for bacteria were negative. The serum calcium was 9.1 mg. % and the phosphorus 3.5 mg. %. The CO_2 was 19 mEq. per liter and the potassium 7.5 mEq. per liter. The latter came down to 5.6 mEq. per liter after intravenous administration of 1,000 cc. of dextrose in water and insulin.

Preterminally the blood pressure rose to 190/150. The optic fundi remained negative. The patient developed moderate edema, but this disappeared after restriction of fluid. The CO_2 fell to 13 mEq. per liter but was restored to 20 mEq. per liter by giving M/6 sodium lactate. He seemed to be getting along fairly well. However, after being allowed up and around, he developed severe convulsions followed by coma and death.

Fig. 3.—Kidneys measuring 3×2×1 cm., weighing a total of 18 gm. The surface is granular and pitted.

An autopsy was performed. The most striking finding was extremely small kidneys. Their total weight was 18 gm., and each measured 3×2×1 cm. The renal artery and vein appeared normal on both sides as did the renal pelvis and upper ureter (Fig. 3). The capsules of both kidneys were firmly adherent. Cut surfaces were dull, yellowish-gray in color, and granular. The corticomedullary

Fig. 4. — Bisection of the kidneys reveals only six minor calyces on the left, whereas only four can be discerned on the right.

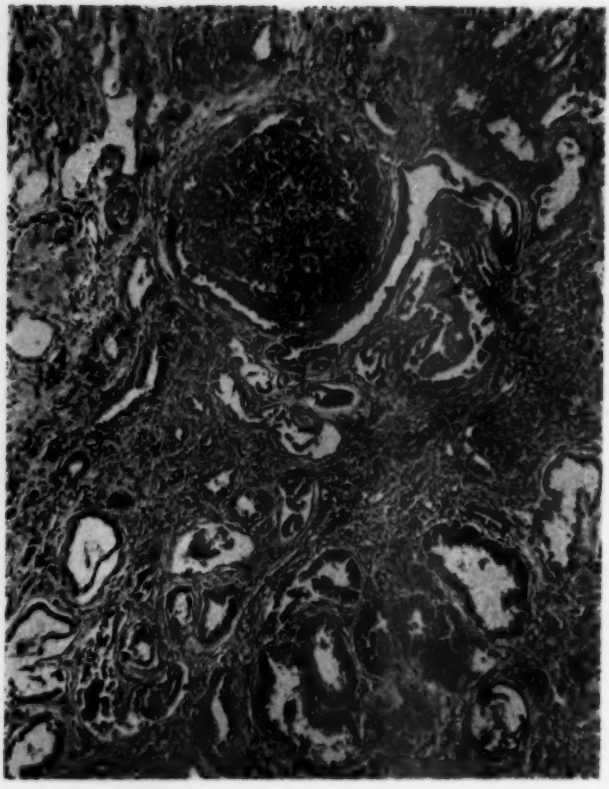

Fig. 5.—Section from kidney revealing proliferation of endothelial cells. There is obliteration of Bowmans space and severe tubular atrophy associated with absent or obstructed glomeruli. There is increased interstitial tissue due to proliferative fibrosis; × 100.

line was almost obliterated. The renal architecture was hardly distinguishable. No cysts, infarcts, petechiae, abscesses, or stones were seen on gross examination. The calyces appeared to be smaller than normal (Fig. 4). The pyramids were later reconstructed in an attempt to determine their exact number. Each kidney had four or five.

The microscopic examination of the kidneys revealed extreme cortical atrophy due to atrophy of the tubules, which in some places were almost absent. The number of glomeruli was greatly reduced, and 95% showed varying degrees of hyalinization. There were no signs of the earlier lesions of glomerulonephritis. A few small foci of lymphocytes were found, mostly in the areas of severe tubular atrophy and replacement fibrosis. The arteries and arterioles in the kidneys showed extensive atrophy, thickening, and attenuation of the lumen, but there was no true hyaline arteriosclerosis or arteriolarsclerosis (Fig. 5).

The parathyroid glands were markedly enlarged, weighing a total of 1.9 gm. Microscopic sections revealed hyperplasia. All four glands showed the same picture. Chief cells and intermediate cell types predominated. Large, clear cells were notably absent, and fat was hardly seen (Fig. 6).

The heart weighed 184 gm. There were no defects or anomalies. All the valves were normal. There were no mural thrombi. The coronaries appeared normal. The left ventricle was markedly hypertrophied. The aorta and its branches in the thorax and abdomen were normal.

The other findings at autopsy were not remarkable.

Comment

Prior to death, various causes for the extremely small kidneys were considered:

1. *Glomerulonephritis or Pyeloncphritis.*

This history of albuminuria during the previous three and one-half years and the presence of a few erythrocytes, azotemia, and an increasing blood pressure indicated an inflammatory process. Absence of an increased number of leukocytes in the urine, negative urine cultures, normal findings on

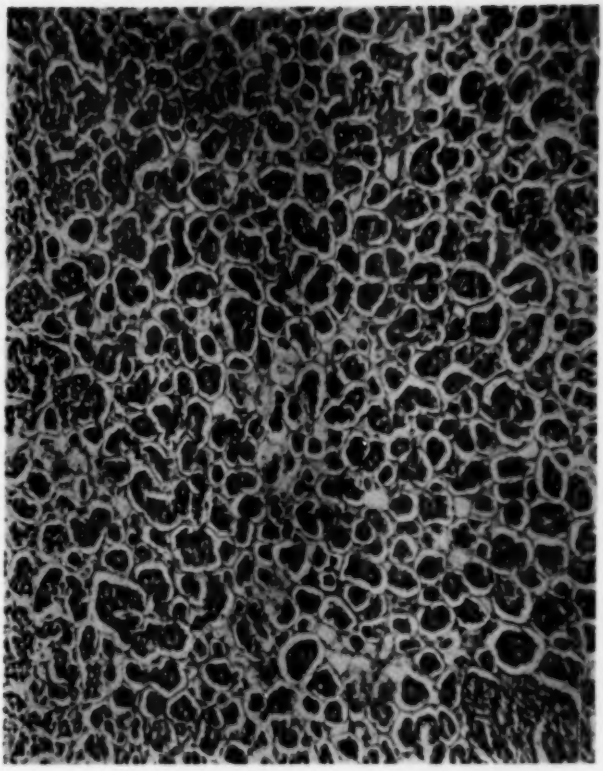

Fig. 6. — Representative area of parathyroid gland. Note predominance of chief cells and intermediate cells along with absence of fat. The conspicuous interstitial component in the photograph is partly formalin fixation artifact; × 60.

cystoscopy, and lack of a history of an acute febrile episode followed by urinary symptoms indicated glomerulonephritis rather than pyelonephritis.

2. *Renal Hypoplasia.* — The extremely small size of the kidneys as seen on pyelography and the decreased number of calyces raised the question of hypoplasia of the kidneys. Characteristic pyelographic patterns have been ascribed to hypoplasia,[1-3] such as absence of major calyces and enlarged, bulbous, triangular, or ampullary pelvis. Caffey,[4] however, includes all the above-mentioned shapes of the renal pelvis among the normal variations. Emmet[5] demonstrated that there is no relationship between pyelographic patterns and pathological appearance of the kidney. No definite diagnosis of renal hypoplasia was therefore made prior to death, but the possibility was kept in mind.

3. *Lipoid-Storage Disease.*—The conspicuous pigmentation and the presence of large numbers of histiocytes and phagocytized lipoid material in the bone marrow made us consider lipoid-storage disease initially. Absence of characteristic involvement of the skeletal system, liver, and spleen and the ensuing clinical course were not characteristic of this disease.

The microscopic picture of the kidneys at autopsy was clearly that of chronic glomerulonephritis. This alone may account for the small size of the kidneys. In the present case, however, the number of pyramids and calyces was decreased. In Bell's[6] series of 213 cases of chronic glomerulonephritis, the smallest kidneys weighed 33 gm. and were found in a 25-year-old man. In an 8-year-old boy the weight of both kidneys was 41 gm. Paetzel,[7] however, states that glomerulonephritis alone rarely pro-

duces really dwarfed kidneys. Mathe [1] and Kempf [8] maintain that atrophic changes are usually found in hypoplastic kidneys, and Campbell [2] states that chronic nephritis is characteristically present in hypoplasia of the kidneys.

Decreased number of pyramids is considered a criterion of renal hypoplasia by Bell [6] and Herbut.[9] Emmet [5] feels that the identification of pyramids is too uncertain to serve as a reliable criterion of hypoplasia.

The decreased number of pyramids and calyces along with the extremely small size of the kidneys indicate that congenital hypoplasia was present in the case under discussion. Retardation of growth was probably present during the first year of life. Glomerulonephritis at this age is rather uncommon. Bell describes two cases of acute glomerulonephritis occurring during the second year of life and two patients with chronic glomerulonephritis dying at the age of 7.

Chronic glomerulonephritis was present in our case but occurred most likely in hypoplastic kidneys. The role of each in producing renal failure is difficult to evaluate.

The greatly enlarged parathyroid glands indicated a state of hyperparathyroidism, provided that enlarged glands also means hypersecretion. Increased number of chief cells and sparsity of fatty tissue presumably indicate increased secretion.[10] Both findings were present in our case.

Various theories exist as to the cause of hypertrophy of the parathyroid glands in renal failure. It is generally believed that a low content of serum calcium is the main stimulus.[11-14] Some authors believe that hyperphosphatemia is the main factor acting to produce a decreased content of calcium.[15] Albright [16] has shown experimentally that ingestion of large amounts of phosphates will produce hyperparathyroidism.

Another theory explains the low serum calcium as being due to increased excretion of calcium in the urine as fixed base instead of ammonia. Acidosis and inability of the kidneys to produce ammonia are the basic factors, according to this theory. It is noteworthy that prolonged acidosis alone may cause hyperplasia of the parathyroid glands as shown by Jaffe.[17] Park and Elliot [18] maintain that a rigid Ca/P balance imposed by the kidneys acts as a stimulus to hypertrophy of the parathyroid glands.

In our case the serum calcium and phosphorus deviated only slightly from normal for five months. This may represent a state of balance developed through several years.

As the disease progressed, however, a low serum phosphorus was found, indicating persisting ability to excrete phosphorus. It is, therefore, not likely that the stimulus to hyperplasia of the parathyroid glands in our case was a high content of serum phosphorus or a rigid Ca/P balance during the last stages of the disease. These conditions may, however, have existed at an earlier time.

Park and Elliot also state that the ultimate cause for stimulation of the parathyroid glands is renal insufficiency. This includes acidosis and oftentimes decreased production of ammonia by the kidneys. In our case the CO_2 content of the blood decreased with increasing blood urea nitrogen and increased amounts of calcium were excreted in the urine. The acidosis theory, therefore, seems to offer the best explanation of the hyperplasia of the parathyroid glands in the present case.

The characteristic finding of hyperparathyroidism is osteitis fibrosa cystica. Radiograms of the skeleton in the present case did not show any cystic lesions, but the granular pattern of the cranial bones was suggestive of hyperparathyroidism. Microscopic examination revealed, furthermore, invasion of bone by fibrous tissue and the presence of numerous osteoblasts and osteoclasts, although no definite cysts could be seen. The changes observed by x-ray of the ribs and wrists were those of rickets, although the trabeculation of the bones was coarser than is usually seen in this disease. Changes characteristic of osteitis fibrosa cystica and rickets may occur side by side in renal

hyperparathyroidism.[19-20] The former is due to increased mobilization of calcium from the bones, the latter to inadequate amounts of calcium being deposited in the growing bones. Coexistence of the two can be explained on the basis of increased excretion of calcium by the kidneys leaving too little calcium available for adequate ossification in spite of increased mobilization of this mineral from the skeleton. The changes observed in the wrists and ribs can therefore also be explained on the basis of renal acidosis. It is unfortunate, however, that no sections of bone from these areas were examined microscopically, as this might have yielded valuable information as to the true nature of the changes observed in the radiograms.

The cause for the suppression of the bone marrow and resulting normochromic anemia is unknown, but both are common in long-standing renal failure from any cause.[21,22] The severity of the anemia closely follows the degree of azotemia, and it belongs to the "hypoplastic-aplastic" group of anemias, most of which have an obscure etiology. Myelofibrosis is often observed in this group of anemias. Increased amount of lipoid material is also seen. This has often been linked to low serum proteins. At times a hemolytic component has been found. Our case shows all these features, but serum proteins were low only shortly before death. The absence of fetal hemoglobin in the peripheral blood along with a severe anemia indicates a poor response from the blood-forming organs. Attempts at therapy with iron and cobalt in the present case were unsuccessful in relieving the anemia.

Summary

A case report of a 10-year-old child dying from renal failure is presented. At autopsy the combined weight of the kidneys was 18 gm. Extensive changes due to glomerulonephritis and decreased number of pyramids were found. It is felt that the cause for dwarfing of the kidneys most likely was glomerulonephritis occurring in hypoplastic kidneys.

Hyperparathyroidism and renal rickets were present. Renal acidosis is probably the best explanation for these changes in the present case.

Marked anemia and hypoplasia of the bone marrow was found. No explanation of the mechanism for these changes can be given.

Gundersen Clinic.

REFERENCES

1. Mathe, C. P.: Diminutive Kidney, California Med. 84:10 (Feb.) 1958.

2. Campbell, M. F.: Clinical Pediatric Urology, Philadelphia and London, The W. B. Saunders Company, 1951.

3. Asbeshouse, B. S.: Congenital Renal Aplasia with Calcified Cystic Degeneration, J. Internat. Coll. Surgeons 26:283 (Sept.) 1956.

4. Caffey, J.: Pediatric X-Ray Diagnosis, Ed. 2, Chicago, The Year Book Publishers, Inc., 1950.

5. Emmet, J. L.; Alvarez-Ierena, J. J., and McDonald, J. R.: Atrophic Pyelonephritis Versus Congenital Renal Hypoplasia, J. A. M. A. 148:1470 (April 26) 1952.

6. Bell, E. T.: Renal Diseases, Philadelphia, Lea & Febiger, 1950.

7. Paetzel, W.: Zwergnieren, Chirurg 27:444 (Oct.) 1956.

8. Kempf, F. K.: Die Nierenaplasie mit Berücksichtigung der Hypoplasie und die Deutung gleichzeitiger cystischer Hamartien im Nieren-lager (Nierenblastemcysten), Arch. path. Anat. 328:182, 1956.

9. Herbut, P. A.: Urological Pathology, Philadelphia, Lea & Febiger, 1952.

10. Castelman, B., and Mallory, T. B.: Parathyroid Hyperplasia in Chronic Renal Insufficiency, Am. J. Path. 13:553 (July) 1937.

11. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, The Williams & Wilkins Company, 1948.

12. Wilkins, L.: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1957.

13. Aegerter, E., and Kirkpatrick, J. A., Jr.: Orthopedic Diseases, Philadelphia and London, The W. B. Saunders Company, 1958.

14. McLean, F. C., and Urist, M. R.: Bone: An Introduction to the Physiology of Skeletal Tissue, Chicago, The University of Chicago Press, 1954.

15. Smyth, F. S., and Goldman, L.: Renal Rickets with Metastatic Calcification and Parathyroid Dysfunction, Am. J. Dis. Child. 48:596 (Sept.) 1934.

16. Albright, F.; Bauer, W.; Claflin, D., and Cockrill, J. R.: Studies in Parathyroid Physiology: The Effect of Phosphate Ingestion in Clinical Hyperparathyroidism, J. Clin. Invest. 11:411 (March)1932.

17. Jaffe, H. L.; Bodansky, A., and Chandler, J. P.: Ammonium Chloride Decalcification, as Modified by Calcium Intake: The Relation Between Generalized Osteoporosis and Ostitis Fibrosa, J. Exper. Med. 56:823 (Dec.) 1932.

18. Park, E. A., and Elliot, M. M.: Renal Hyperparathyroidism with Osteoporosis (Osteitis) Fibrosa Cystica, in Brenneman's Practice of Pediatrics, edited by I. M. McQuarrie, Hagerstown, Md., W. F. Prior Company, Inc., 1936, Vol. 3, Chap. 29.

19. Langmead, F. S., and Orr, J. W.: Renal Rickets Associated with Parathyroid Hyperplasia, Arch. Dis. Childhood 8:265 (Aug.) 1933.

20. Pappenheimer, A. M.: The Effect of Experimental Reduction of Kidney Substance upon the Parathyroid Glands and Skeletal Tissue, J. Exper. Med. 64:965 (Dec.) 1936.

21. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1956.

22. Wolff, J. A.: Anemias Caused by Infections and Toxins, Idiopathic Aplastic Anemia and Anemia Caused by Renal Disease, Pediat. Clin. North America 4:469 (May) 1957.

The Concentration of Potassium in the Plasma

Studies of Clinically Well Premature Infants Given Formulas of Varying Mineral Composition

HANS G. KEITEL, M.D., Philadelphia
With the Technical Assistance of Jocelyn Blakely

In the present report the plasma potassium concentration of premature infants of varying ages and weight is presented and the range of the "normal" concentrations established, taking into account the effect of the dietary intake and the age of the subjects.

The potassium content of a formula for feeding the premature infant was changed by altering the carbohydrate content of the formula and by adding various salts of sodium, potassium, and calcium. The effect of these changes on the plasma concentration of potassium was observed.

The data obtained are interpreted to indicate that the factors which affect the plasma concentration of potassium in the premature infant appear similar to those which have been identified in the adult.

Patient Material

Clinically well infants were studied. Infants weighing less than 5½ lb. (2.5 kg.) at birth were considered to be premature. The temperature of the nursery was maintained between 24 and 27 C. Babies weighing less than 3½ lb. (1.6 kg.) were usually placed in an "isolette," the temperature being kept between 28 and 33 C and the humidity between 60% and 95%. Oxygen was occasionally administered, but babies with pronounced respiratory insufficiency or other major complications were not included in the study.

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Feeding Routines

Between the 12th and 18th hour of life 5 to 10 cc. of 5% glucose was offered. On the second day the premature infants were fed formula No. 3 every three hours, the amount depending on the appetite (modified self-demand feeding). Babies requiring gavage were not included in the study. Vitamin C, 50 mg.; vitamin D, 500 units, and vitamin A, 2,500 units, were given daily to all infants after the third day of life.

Babies weighing over 5½ lb. were considered to be full term, and were fed formula No. 1 every four hours after the first day of life. They received the same vitamin supplements as the premature infants (*vide supra*).

The potassium bicarbonate, sodium bicarbonate, and calcium gluconate formulas are formula No. 3 to which was added 1 mM per bottle of the respective salt. The "high" and "low" carbohydrate formulas will be referred to as the high and low "CHO" formulas. The potassium, total mineral, and protein content of the high "CHO" formula is lower than formula No. 3, while that of the low "CHO" formula is higher than formula No. 3 (Table). After the fifth day of life the intake of the infants in cubic centimeters per kilogram of body weight ranged from 120 to 190 per day, and, except for the babies receiving sodium bicarbonate, the weight gain of infants receiving the various formulas was similar. The infants to whom sodium bicarbonate was administered gained more weight, although the caloric intake was comparable. This has been shown to be the result of the retention of edema fluid.[1] The infants re-

Calculated Composition of the Formulas Used in the Present Study Relative to Human Milk and Unmodified Cows' Milk

Content Per 100 Cc.	Formula *		Low CHO	High CHO	Human Milk	Cows' Milk
	1	3				
Na, mM	1.4	2.5	3.6	1.4	0.5	2.7
K, mM	2.4	4.7	6.7	2.7	1.3	3.9
Cl, mM	1.6	1.8	2.6	1.0	1.0	3.3
Ca, gm.	0.100	0.104	0.148	0.059	0.034	0.122
P, gm.	0.07	0.078	0.109	0.044	0.015	0.09
Protein, gm.	2.6	3.1	4.4	1.8	1.3	3.5
Fat, gm.	2.9	1.2	1.7	0.68	3.5	3.5
Carbohydrate, gm.	3.7	8.3	5.6	10.8	7.5	4.8
Calories	56	76	55	56	66	66

*Dryco was the milk base used.

ceiving the high "CHO" diet received from 2.7 to 3.4 gm. of protein per kilogram per day, the infants on the low "CHO" diet from 5.7 to 6.4 gm. protein per kilogram, and those on formula No. 3 from 4.2 to 4.8 gm. per kilogram per day. Blood samples were taken after the infants had received the various formulas from four to seven days. Evidence of intolerance was not noted except in two infants receiving the low "CHO" formula.

Blood Sampling

Blood samples were obtained two to three hours postprandial. Approximately 5 cc. of blood was drawn from the external or internal jugular vein into oiled silicone-coated syringes containing a trace (less than 0.02 cc.) of isotonic heparin (Upjohn, 10,000 units per cubic centimeter). In vitro hemolysis was minimized by preventing foaming, by not exposing the blood to excessive negative or positive pressure, and by using a new needle after an unsuccessful venipuncture. The samples were immediately transferred to 10 cc. test tubes, stoppered, and within 15 minutes were centrifuged for 20 minutes at 2,000 rpm at a distance of 15 cm. from the center of gyration. After centrifugation the plasma was pipetted into a separate tube, care being taken not to include buffy coat elements, which contain a high concentration of potassium and phosphorus.[2]

The plasma potassium concentration was determined by the Flame Photometric Method, as described elsewhere.[3] In a Normax volumetric flask with triple distilled water 0.5 cc. of plasma was diluted to 10 cc. Replicate samples revealed an accuracy within ±3%. The concentration of potassium in the plasma of fasting normal adults using this method was found to be 4.3 mM/L plasma with a standard deviation of 0.25.[3]

A possible source of error in the determination of the plasma potassium concentration is the liberation of potassium into plasma from lysed red blood cells, white cells, or platelets. To evaluate the possible magnitude that the lysis of red cells raised the potassium concentration, the plasma hemoglobin concentration was determined in the majority of samples analyzed for potassium. These data, which appear in Figure 1, indicate that the plasma hemoglobin concentration is higher in the first two weeks of life, during which time the hematocrit

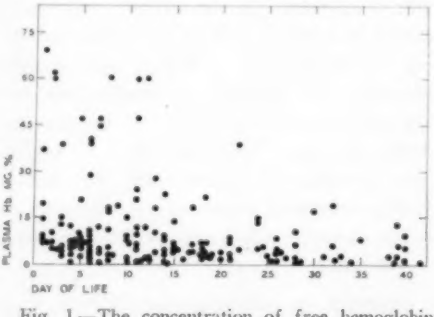

Fig 1.—The concentration of free hemoglobin in the plasma of premature infants at varying ages.

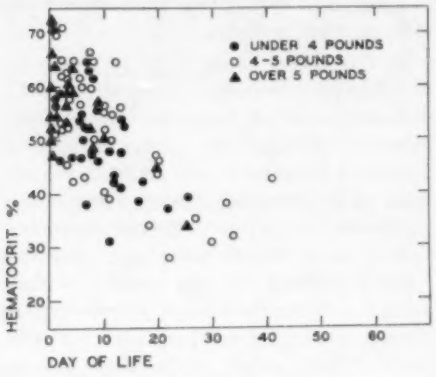

Fig. 2.—The hematocrit values of premature infants at varying ages.

value fell rapidly (Fig. 2). As most plasma hemoglobin values were found to be below 50 mg. %, the amount of potassium which could have come from lysed red cells could not have raised the potassium concentration of plasma more than about 0.2-0.3 mM per liter. If the hemoglobinemia did not result from the venipuncture, and resulted from in vivo hemolysis, the plasma potassium concentration would hardly have been raised at all, since the liberated potassium would have equilibrated with the entire extracellular space rather than with the plasma volume alone.

The concentration of potassium was found to be the same after blood samples were collected and centrifuged in ordinary glass tubes and in silicone-coated glass tubes.

The in vitro storage at room temperature of unclotted blood of adults results in very little or no change in the potassium concentration of the plasma within two hours (Fig. 3). Since the blood of infants usually contains a higher percentage of nucleated red blood cells and white cells than does blood from adults, it seemed appropriate to observe the magnitude of change in plasma potassium concentration which occurs at various time intervals following the procurement of heparinized blood from infants. The blood samples were stored in a stoppered oiled syringe at room temperature (24 C) and were gently mixed every five minutes. Aliquots were removed and centrifuged at the time intervals as indicated in Figure 3. The concentration fell from 0.1-0.2 mM per liter in the first 60 minutes in most instances.

On the basis of the above findings, it is assumed that the potassium data to be reported represent primarily the in vivo status of the potassium concentration of plasma.

Results

The statistical analysis of the data to be presented are contained in the addendum.

A. The Plasma Potassium Concentration at Varying Times After Delivery.—The plasma potassium concentration of full-term infants during the first week of life extends from 3.6 to 5.6 mM per liter, with most values falling in the normal adult range of 3.7 to 5.0 mM per liter (Fig. 4). In the case of the premature infants, the plasma potassium concentration is in the normal adult range only on the first few days of life (Fig. 5). Thereafter, the average value gradually rises, being on the average 5.3 mM per liter on about the sixth day with little change thereafter. Out of over 100 determinations, 4 were observed to be in

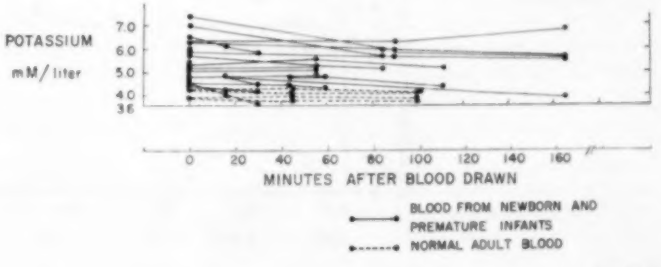

Fig. 3.—The changes in the plasma potassium concentration when uncentrifuged blood of premature infants stands at room temperature (23-26 C) for varying periods of time following removal from the body.

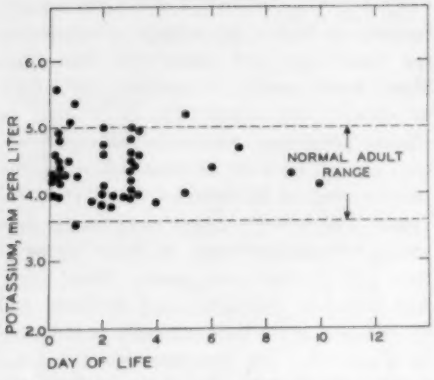

Fig. 4.—The plasma potassium concentration of full-term infants fed formula No. 1.

excess of 6 mM per liter. There is no indication that the values in the premature infants weighing less than 4 lb. (1.8 kg.) differ from the premature infants weighing over 4 lb. Only one value below the normal adult range was found in the premature infants. Since the potassium intake of the premature infant is almost double that of the full-term infant, it can not be inferred that the reason that the potassium concentration of plasma of the full-term infants is lower than that of the premature infant is because of "maturity."

B. The Effect of the Type of Intake on the Plasma Potassium Concentration.—1. Administration of Potassium Bicarbonate: When 8 mM per day (3-6 mM/kg.) of potassium bicarbonate was added to the formula of 23 premature infants, a statistically significant rise in the potassium concentration occurred, the elevation being somewhat more prominent in the smaller infants (Fig. 6). Since the smaller infants received almost twice as much potassium per kilogram of body weight as the larger infants, the greater rise could be attributed to the larger dose per unit of body weight.

2. The Effect of the Administration of a High-Carbohydrate, Low-Protein-Ash-Content Formula, and a Low-Carbohydrate, High-Protein-Ash-Content Formula: When a high carbohydrate (low ash and protein) content formula was administered to 21 premature infants, a small drop, on the average 0.3 mM per liter, in the plasma potassium concentration was observed (Fig. 6). The administration of the *low* carbohydrate (high ash and protein) content formula to 28 pre-

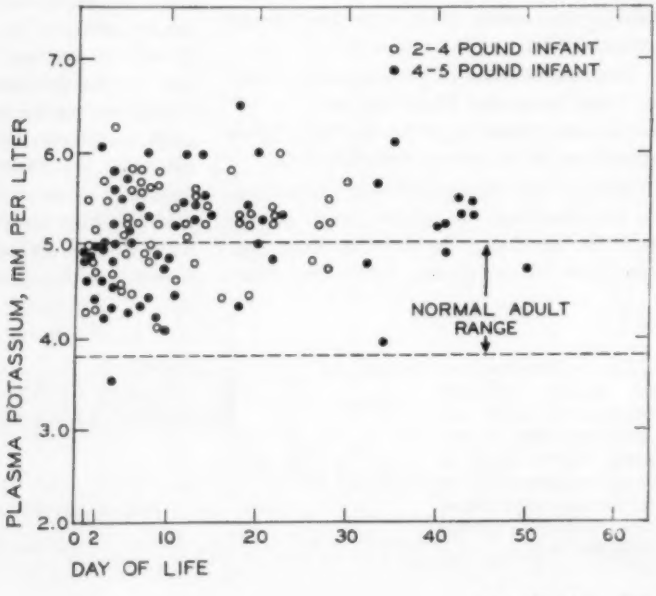

Fig. 5.—The concentration of potassium in the plasma of premature infants fed formula No. 3.

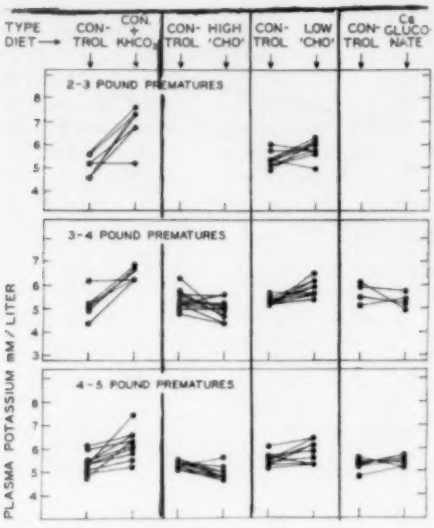

Fig. 6.—The potassium concentration of plasma of premature infants fed different formulas (see methods for the composition of the formula used).

mature infants resulted in an average rise of about 0.3 mM per liter in the plasma potassium concentration (Fig. 6). The changes were statistically significant.

3. Administration of Calcium Gluconate: The administration of 8 mM per day of calcium gluconate did not result in a statistically significant change in the potassium concentration of plasma in the 10 infants who were studied (Fig. 6).

Comment

The concentration of potassium in the plasma of infants has previously been reported as being both very high and low, although most reports reveal values that are only slightly elevated, compared with normal adult values.[5-8] From the results of the present study it would appear that very low values (less than 3.5 mM/L) or high values (more than 6.2 mM/L) may indicate the presence of disturbed metabolism of potassium, since values between 3.8 to 6.2 mM per liter were found in premature infants of all ages and maturity when from 4 to 9 mM of potassium per kilogram per day was ingested. Some of the high potassium values previously reported were found in placental blood.[7] It cannot be assumed that the plasma potassium concentration of placental blood necessarily represents the in vivo potassium concentration of plasma of the fetus since the length of time of separation of the placenta, stasis, and CO_2 accumulation may markedly affect potassium concentration.

Large amounts of potassium can be excreted quite satisfactorily in the very small premature infant; for example, the infants weighing from 2-3 lb. (0.9 to 1.4 kg.) who were given potassium bicarbonate supplements received 13 mM of potassium per kilogram per day. It is probable that adults who ingest a comparable amount of potassium * might also have plasma potassium concentrations above the normal range. Tudvad, McNamara, and Barnett [10] had already demonstrated that the premature can excrete acutely administered potassium loads fairly promptly, and that more potassium can be excreted than is filtered by the glomerulus.

When the data obtained on the various formulas are plotted to show the relationship of the potassium intake, millimoles per kilogram, to the plasma potassium concentration, millimoles per liter, it is seen that the plasma potassium concentration is directly correlated with the dietary intake of potassium (Fig. 7). If the line joining the data obtained is extended, the plasma potassium concentration would be expected to be about 4.6 mM/L when 2 mM of potassium per kilogram per day is ingested.

The full-term infant, who had an average intake of potassium of about 3 mM/kg. per day, had an average plasma potassium concentration of 4.7 mM per liter.

Burnell, Villamil, Uyeno, and Scribner [4] have reported that the plasma potassium concentration increases when the pH of blood is reduced. Since the premature infant has about an 0.04-0.08 unit lower blood pH than

* It would be hard to decide whether a comparable dose for the adult would be about 13/3=4.1 mM/kg.—i. e., a "body surface" corrected amount—or another dose.

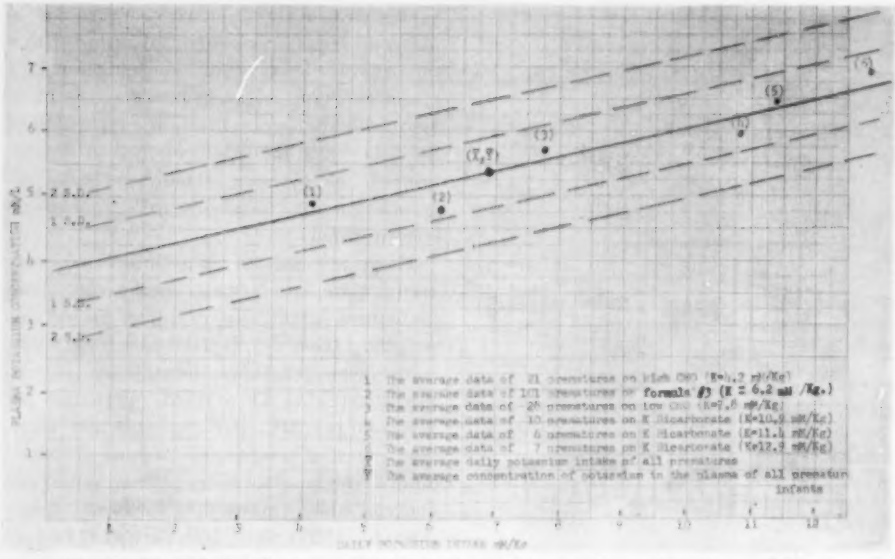

Fig. 7.—The relationship between the daily intake of potassium, millimoles per kilogram, and the concentration of potassium in the plasma of premature infants, millimoles per liter.

the adult, his average potassium concentration would be about 4.8 mM/L rather than 5.2, if the correction for acidosis, as indicated by Burnell et al.,[4] is made.

Summary and Conclusion

The concentration of potassium in the plasma of premature infants of varying ages ranging in weight from 2 to 5 lb. (0.9 to 2.3 kg.) was determined, using a standardized method of procuring, separating, and analyzing the blood samples, and taking special note of the intake of potassium.

The plasma potassium concentration was found to be directly correlated with the potassium intake.

In the first two days of life, most potassium values were in the same range as that found for normal fasting adults.

The plasma potassium concentration of normal premature infants receiving an intake of potassium of about 6 mEq. per kilogram would be expected to range from about 4 to 6 mEq. per liter after the third day of life.

Dr. Roland Scott, of the Freedman's Hospital, Washington, D. C., gave advice and help in this study.

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REFERENCES

1. Young, W. F.; Hallum, J. L., and McCance, R. A.: The Secretion of Urine by Premature Infants, Arch. Dis. Childhood 16:243, 1941.

2. Keitel, H. G., and Jones, H., unpublished data.

3. Keitel, H. G.; Berman, H.; Jones, H., and MacLachlan, E.: The Chemical Composition of Normal Human Red Blood Cells, Including Variability among Centrifuged Cells, J. Hemat. 4:370, 1955.

4. Burnell, J. M.; Villamil, M. F.; Uyeno, B. T., and Scribner, B. H.: The Effect in Humans of Extracellular pH Change on the Relationship Between Serum Potassium Concentration and Intracellular Potassium, J. Clin. Invest. 35:935, 1956.

5. Natelson, S.: Correlation of Clinical and Chemical Observations in the Immature Infant: Manual for Physicians and Chemists, Munson Printing Company, 1952.

6. McCance, R. A., and Young, W. F.: The Secretion of Urine by Newborn Infants, J. Physiol. 99:265, 1941.

7. Edelstein, F., and Ylppö, A.: Passage of Salts Through the Placenta, Ztschr. Kinderh. 27: 79, 1920.

8. Pincus, J. B.; Gittleman, I. F.; Saito, M., and Sobel, A. E.: A Study of Plasma Values of Sodium, Potassium, Chloride, Carbon Dioxide,

Carbon Dioxide Tension, Sugar, Urea and the Protein Base-Binding Power, pH and Hematocrit in Prematures on the First Day of Life, Pediatrics 18:39, 1956.

9. McCance, R. A., and Widdowson, E. M.: The Correct Physiological Basis on Which to Compare Infant and Adult Renal Function, Lancet 2:860, 1952.

10. Tudvad, F.; McNamara, H., and Barnett, H. L.: Renal Response of Premature Infants to Administration of Bicarbonate and Potassium, Pediatrics 13:4, 1954.

Addendum

Statistical Analysis of Infants Fed Diets Containing Various Levels of Potassium

Diet	Composition of Sample	Number of Infants	Mean Change Plasma K mEq/L	Standard Deviation	Standard Error	t	P	Significant ● P <0.05
High CHO	All infants <5 lbs.	21	−0.35	±0.42	±0.009	3.89	<0.001	Yes
Calcium gluconate	All infants <5 lbs.	10	−0.09	±0.29	±0.09	1.00	<0.40	No
Low CHO	All infants <5 lb.	28	+0.39	±0.46	±0.09	4.33	<0.001	Yes
K bicarbonate	All infants <5 lb.	23	+1.12	±0.88	±0.18	6.22	<0.0001	Yes
High CHO	Infants 3-4 lb.	11	−0.31	±0.49	±0.15	2.07	<0.10	No
High CHO	Infants 4-5 lb.	10	−0.39	±0.34	±0.11	3.55	<0.01	Yes
Calcium gluconate	Infants 3-4 lb.	4	−0.28	±0.51	±0.26	1.08	<0.30	No
Calcium gluconate	Infants 4-5 lb.	6	+0.03	±0.30	±0.12	0.25	<0.90	No
Low CHO	Infants 2-3 lb.	9	+0.38	±0.54	±0.18	2.11	<0.10	No
Low CHO	Infants 3-4 lb.	10	+0.50	±0.43	±0.14	3.57	<0.01	Yes
Low CHO	Infants 4-5 lb.	9	+0.29	±0.43	±0.14	2.07	<0.10	No
K bicarbonate	Infants 2-3 lb.	7	+1.76	±0.89	±0.34	5.18	<0.005	Yes
K bicarbonate	Infants 3-4 lb.	6	+1.23	±0.65	±0.27	4.56	<0.01	Yes
K bicarbonate	Infants 4-5 lb.	10	+0.61	±0.71	±0.22	2.77	<0.025	Yes

Addendum continued on page 90/590.

Statistical Analysis of the Relationship Between the Daily Intake of Potassium, Millimole per Kilogram, and the Concentration of Potassium in the Plasma of Premature Infants, Millimole per Liter

All Infants

	Potassium Intake X	Potassium Plasma Y
N (no. of infants)	173	173
$\overline{X}$ (mean)	6.94 mM/Kg.	5.34 mM/L
σx (standard deviation)	2.1 mM/Kg.	0.71 mM/L

r = 0.65

r (coefficient of correlation, ±1 = perfect correlation) = 0.65

Regression equation: Yc = 3.81+0.22X

Sy (a measure comparable to standard deviation) = 0.54

Of the 173 infants in this experiment, 101 were fed a standard diet of 6.2 mM/Kg. This obviously weights the results toward "normalcy." Omitting babies fed formula No. 3 provides the following, including a higher degree of correlation, a very minimal change in the regression equation, and a smaller scatter (or S. D.):

	X	Y
N	72	72
$\overline{X}$	7.98 mM/Kg.	5.68 mM/L
σx	2.69 mM/Kg.	0.74 mM/L

r = 0.83

Regression equation

Regression equation: Yc = 3.86+0.23 X

Sy = 0.41

	Diet 1	Diet 2	Diet 3	Diet 4	Diet 5	Diet 6
	4.2 mM/Kg.	6.2 mM/Kg.	7.8 mM/Kg.	10.9 mM/Kg.	11.4 mM/Kg.	12.9 mM/Kg.
N	21	101	28	10	6	7
$\overline{Y}$ (mean K plasma)	4.93 mM/L	4.77 mM/L	5.70 mM/L	5.94 mM/L	6.43 mM/L	6.87 mM/L

Kernicterus in Rats with an Inherited Deficiency of Glucuronyl Transferase

LOIS JOHNSON, M.D.; FELICITAS SARMIENTO, M.D.; WILLIAM A. BLANC, M.D., and RICHARD DAY, M.D., New York

This paper describes the occurrence of kernicterus and factors which influence its development in the strain of rats * first studied by Gunn.[22,23] The disease of humans designated in 1903 by Schmorl [39] as kernicterus has, in our opinion, not been observed or induced in its entirety in animals. Various workers, however, have demonstrated the toxicity of indirect bilirubin.[12-15,24,26,44-46] Ernster, Herlin, and Zetterström [21] have caused localized pigmentation of the brain of the rabbit by treatment with bilirubin and an S-H blocking agent. Other workers [17,19,20] have reported injury of brain tissue in hemolytic anemia of animals, a phenomenon not directly related to the present report, since the rats to be described do not suffer from antibody-antigen disease and have little or no hemolytic anemia.

Definition of Kernicterus

The following criteria are proposed as defining kernicterus:

1. Distinctive evidence of central nervous system dysfunction during life in jaundiced subjects
2. Canary yellow staining of nuclear masses of brain, or spinal cord, or both, in postmortem specimens
3. Persistence of the yellow color for several weeks when the brain is fixed in formalin, without the appearance of a permanent green color as in most other icteric tissues
4. The presence of intracellular pigment in frozen sections
5. Evidence of degeneration of nerve cells in specimens prepared for microscopic examination

A presumptive diagnosis of kernicterus is reasonable in living subjects with jaundice or a past history of jaundice if they display characteristic nervous abnormalities. The diagnosis is strongly supported if at autopsy abnormalities are found in those areas usually stained in subjects dying during the acute episode.

Review of Literature

Gunn's reports [22,23] in 1938 and 1944 indicate that the jaundice in these rats is of the acholuric type. The disease was considered by him to be the expression of a spontaneous mutation. Although the phenotypic inheritance pattern was consistent with that of a single recessive gene,† various considerations led Gunn to believe that the jaundice trait was governed by a dominant gene with incomplete penetrance. In homozygous jaundiced animals he found stunting of growth, a wobbly gait, and a slight anemia. The nervous system disorder seemed to be proportionate to the stunting of growth. Gunn also felt that there was an abnormality of the red cells leading to red cell destruction and jaundice.

Submitted for publication July 30, 1958.

Holder of a National Foundation for Infantile Paralysis Fellowship (Dr. Johnson).

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From the Department of Pediatrics of the State University of New York, Downstate Medical Center, and the Department of Pathology, College of Physicians and Surgeons, Columbia University.

* This strain appeared in 1934 in the breeding stock of the Connaught Laboratories, Toronto, Canada, apparently as the result of a mutation. It has been maintained by Dr. W. E. Castle, from whom we and others have obtained a colony.

† Our observations in this regard duplicate those of Gunn, as is seen in Table 1.

Statistical Analysis of the Relationship Between the Daily Intake of Potassium, Millimole per Kilogram, and the Concentration of Potassium in the Plasma of Premature Infants, Millimole per Liter

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Regression equation: Yc = 3.81+0.22X

Sy (a measure comparable to standard deviation) = 0.54

Of the 173 infants in this experiment, 101 were fed a standard diet of 6.2 mM/Kg. This obviously weights the results toward "normalcy." Omitting babies fed formula No. 3 provides the following, including a higher degree of correlation, a very minimal change in the regression equation, and a smaller scatter (or S. D.):

	X	Y
N	72	72
$\overline{X}$	7.98 mM/Kg.	5.68 mM/L
σx	2.69 mM/Kg.	0.74 mM/L

r = 0.83

Regression equation

Regression equation: Yc = 3.86+0.23 X

Sy = 0.41

	Diet 1	Diet 2	Diet 3	Diet 4	Diet 5	Diet 6
	4.2 mM/Kg.	6.2 mM/Kg.	7.8 mM/Kg.	10.9 mM/Kg.	11.4 mM/Kg.	12.9 mM/Kg.
N	21	101	28	10	6	7
$\overline{Y}$ (mean K plasma)	4.93 mM/L	4.77 mM/L	5.70 mM/L	5.94 mM/L	6.43 mM/L	6.87 mM/L

Kernicterus in Rats with an Inherited Deficiency of Glucuronyl Transferase

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This paper describes the occurrence of kernicterus and factors which influence its development in the strain of rats * first studied by Gunn.[22,23] The disease of humans designated in 1903 by Schmorl [39] as kernicterus has, in our opinion, not been observed or induced in its entirety in animals. Various workers, however, have demonstrated the toxicity of indirect bilirubin.[12-15,24,26,44-46] Ernster, Herlin, and Zetterström [21] have caused localized pigmentation of the brain of the rabbit by treatment with bilirubin and an S-H blocking agent. Other workers [17,19,20] have reported injury of brain tissue in hemolytic anemia of animals, a phenomenon not directly related to the present report, since the rats to be described do not suffer from antibody-antigen disease and have little or no hemolytic anemia.

Definition of Kernicterus

The following criteria are proposed as defining kernicterus:

1. Distinctive evidence of central nervous system dysfunction during life in jaundiced subjects
2. Canary yellow staining of nuclear masses of brain, or spinal cord, or both, in postmortem specimens
3. Persistence of the yellow color for several weeks when the brain is fixed in formalin, without the appearance of a permanent green color as in most other icteric tissues
4. The presence of intracellular pigment in frozen sections
5. Evidence of degeneration of nerve cells in specimens prepared for microscopic examination

A presumptive diagnosis of kernicterus is reasonable in living subjects with jaundice or a past history of jaundice if they display characteristic nervous abnormalities. The diagnosis is strongly supported if at autopsy abnormalities are found in those areas usually stained in subjects dying during the acute episode.

Review of Literature

Gunn's reports [22,23] in 1938 and 1944 indicate that the jaundice in these rats is of the acholuric type. The disease was considered by him to be the expression of a spontaneous mutation. Although the phenotypic inheritance pattern was consistent with that of a single recessive gene,† various considerations led Gunn to believe that the jaundice trait was governed by a dominant gene with incomplete penetrance. In homozygous jaundiced animals he found stunting of growth, a wobbly gait, and a slight anemia. The nervous system disorder seemed to be proportionate to the stunting of growth. Gunn also felt that there was an abnormality of the red cells leading to red cell destruction and jaundice.

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* This strain appeared in 1934 in the breeding stock of the Connaught Laboratories, Toronto, Canada, apparently as the result of a mutation. It has been maintained by Dr. W. E. Castle, from whom we and others have obtained a colony.

† Our observations in this regard duplicate those of Gunn, as is seen in Table 1.

Somewhat different conclusions as to the cause of the jaundice were drawn by Malloy and Lowenstein[31] in 1940 after an extensive study. Although they found a slight, unexplained, normocytic anemia, it was unrelated in severity to the degree of jaundice. In fact, increased resistance to hemolysis by saponin was demonstrated. Observations on jaundiced rats whose bile ducts had been tied off led these workers to conclude that the defect was actually in the excretion of bilirubin. They postulated that the livers of the affected rats were not able to convert the bilirubin which reacted indirectly with diazotized sulfanilic acid to that giving the direct reaction. They further postulated that under ordinary circumstances such conversion was necessary for excretion.

Work in several laboratories has now clarified many of the differences between direct and indirect reacting bilirubin and has also located the enzymatic defect in the genetically jaundiced rats.[2,3,6,27,36-38,43]

Direct reacting bilirubin is a glucuronide of bilirubin. This conjugation with glucuronic acid renders the lipid-soluble bilirubin water-soluble and capable of diazotization in an aqueous solution without the addition of an agent such as alcohol. The metabolic pathway of glucuronide synthesis for steroid and nonsteroid compounds, such as bilirubin and many alcohols and phenols (designated as ROH), appears to be the same, and, according to the work of several authorities, does not involve preformed glucuronic acid.[18,25,29,30,41,42] The steps by which this synthesis occurs can be summarized as follows:

glucose-1-phosphate + uridine triphosphate	uridyl transferase ⟷	uridinediphosphoglucose (UDPG) + pyrophosphate
UDPG	UDPG dehydrogenase ⟷ DPN	uridinediphosphoglucuronic acid (UDPGA)
UDPGA+ROH	glucuronyl transferase ⟶	R-glucuronide + UDP

The livers of the Gunn rats have been shown by Carbone and Grodsky,[6] Schmid et al.,[38] and Lathe et al.[27] to be deficient in glucuronyl transferase activity. The activity of the enzyme is minimal in homozygous animals and decreased to a significant degree in heterozygotes. However, the serum bilirubin levels in the heterozygous rats are normal.

Methods

Bilirubin was determined by the Malloy and Evelyn[22] modification of the van den Bergh procedure. Fifty lambdas of serum was used. The final dilution of serum after addition of all reagents was 1-40. Alcohol was doubly distilled. Exposure to light was minimized.

Blood was collected directly in microhematocrit tubes. Centrifugation was for 15 minutes at 2,500 rpm.

Sulfadiazine and sulfisoxazole levels were determined on 100λ of blood by the method of Bratton and Marshall.[4]

The method of obtaining blood requires some comment. In young rats, even the small quantity of blood needed is a substantial portion of the total blood volume and is best obtained by nicking the femoral vein or artery.‡ Specimens were taken from different rats on different days, the same rat being bled only at well-spaced intervals. Rats under one day of age were killed after bleeding. From age 15 days on, the tail was used as a source of blood.

Terminology

The jaundice gene is identified by the small letter j and the normal gene by the

‡ With practice this can be done without injuring the femoral nerve. However, observations on the clinical manifestations of kernicterus reported in this paper were made on rats never bled in this way.

TABLE 1.—*Inheritance Pattern of Jaundice Gene* in the Colony of Gunn Rats*

Mating Jj×Jj					
Theoretical for a Recessive Trait		Observations of Gunn		Our Observations	
Nonjaundiced	Jaundiced	Nonjaundiced	Jaundiced	Nonjaundiced	Jaundiced
		182 rats	50 rats	336 rats	97 rats
75%	25%	78.4%	21.5%	77.5%	22.5%
Mating Jj×jj					
Theoretical for a Recessive Trait		Observations of Gunn		Our Observations	
Nonjaundiced	Jaundiced	Nonjaundiced	Jaundiced	Nonjaundiced	Jaundiced
		120 rats	113 rats	229 rats	235 rats
50%	50%	51.5%	48.5%	49.3%	50.7%

* jj indicates a homozygous, jaundiced animal; Jj indicates a heterozygous, nonjaundiced animal; JJ indicates a homozygous, nonjaundiced normal animal.

capital letter J. Jaundice occurs only in subjects which are jj in genetic constitution, thus justifying the notation customary for recessive traits.

Results

The Bilirubin Levels in Adult Animals.—Malloy and Lowenstein found the adult rats of the Gunn strain to have an average total serum bilirubin level of 6.1 mg/100 ml. Twenty-seven of our adult jj rats had an average level of 6.33 mg/100 ml., with a standard deviation of the series of 1.47. Nineteen homozygous normal (JJ) rats and 18 heterozygous (Jj) rats had identical mean indirect serum bilirubin levels of 0.21 mg/100 ml., with a standard deviation in each case of 0.16. The bilirubin was almost entirely of the type giving the indirect van den Bergh reaction.

As described later, adult animals occasionally had sudden increases in the level of bilirubin in their sera, conceivably induced by intercurrent infections.

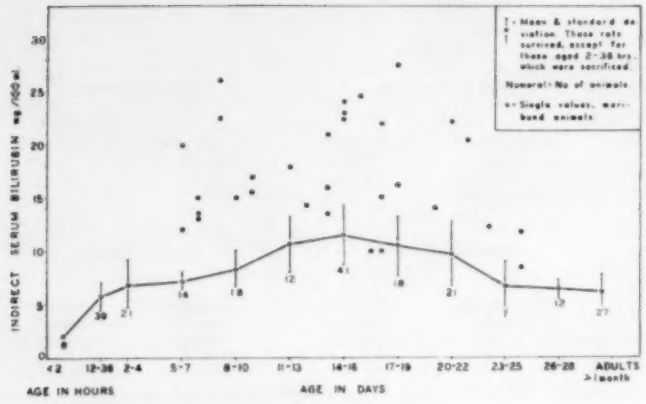
Bilirubin Levels at Birth.—None of the animals was ever observed to be jaundiced immediately after birth, and serum bilirubin determinations were consistent with this observation as shown in Table 2. When blood is withdrawn within two hours of birth the animal has to be killed. Hence, when the mating is one which should produce a mixed litter, separate identification of each newborn as a JJ, Jj, or jj is not possible. Table 2 is accordingly arranged so that the expected number in each category is indicated. The table shows that the level of bilirubin of the mother has little, if any, effect on that of the newborn.

The rise in bilirubin concentration after delivery of the animal is rapid, and by 6 hours of age most newborns are obviously

TABLE 2.—*Indirect Serum Bilirubin (SB) Values of Mothers and Their Young Within Two Hours After Birth in Mg/100 Ml.*

Mating of jj Father and Jj Mother: 50% of Young Expected to Be jj (Jaundiced)	
Litter 137 Mother: SB=0.2	Young: SB=0.2, 0.4, 0.6, 0.4, 0.5, 0.4, 0.4
Litter 144 Mother: SB=0.0	Young: SB=0.9, 0.1, 0.0, 0.6, 0.1 0.9, 0.0, 0.6, 0.2, 0.9
Litter 132 Mother: SB=0.2	Young: SB=2.2, 2.6, 0.9
Mating of Jj Father and jj Mother: 50% of Young Expected to Be jj (Jaundiced)	
Litter 130 Mother: SB=5.0	Young: SB=0.8, 0.3, 0.8, 1.3, 1.3, 0.8
Mating of jj Father and jj Mother: 100% of Young Must Be jj (Jaundiced)	
Litter 151 Mother: SB=5.2	Young: SB=1.9, 2.0, 1.6, 2.7, 2.4
Litter 150 Mother: SB=8.9	Young: SB=3.0, 2.6, 1.6
Litter 218 Mother: SB=9.8	Young: SB=2.0, 2.6
Mating of JJ Parents (Normal Young with Regard to the Jaundice Gene)	
Litter Y Mother SB=0.0	Young: SB=0.2, 0.2, 0.0, 0.0, 0.1, 0.2, 0.0
Litter C Mother: SB=0.4	Young: SB=0.5, 0.4, 0.6, 0.3, 0.2, 0.0, 0.2

jj indicates a homozygous, jaundiced animal; Jj indicates heterozygous, nonjaundiced animal; JJ indicates a homozygous normal, nonjaundiced animal.



Graph 1.—Pattern of indirect serum bilirubin during the first month of life in jj (jaundiced) rats. Animals which die (dots) have much more jaundice than those which survive (circles) with rare exceptions.

jaundiced. Had blood been drawn within a few minutes of birth, bilirubin levels might have been lower than those recorded in Table 2.

Assays of glucuronyl transferase activity were performed in livers removed from homozygous rats which were killed at 12 hours, and 5, 14, and 27 days. The enzymatic activity was markedly decreased as compared with that of normal rat liver, and there was no well-defined relationship to the serum bilirubin concentration.§

The Newborn Period.—An exaggeration of the hyperbilirubinemia occurs in the first month of life, reminiscent, except for its delayed appearance, of the physiologic jaundice of human infants, particularly of premature human infants. Graph 1 shows that approximately a month passes before the bilirubin stabilizes at adult levels.

§ These assays were done by Dr. Irwin Arias of Albert Einstein College of Medicine.

TABLE 3.—*Hematocrit Values During the First Three Weeks of Life in Rats Which Had Not Been Bled Previously*

	Jaundiced (jj)		Nonjaundiced (Jj or JJ)	
Age	No. of Rats	Hematocrit, %	No. of Rats	Hematocrit, %
12-48 hours	38	46.5±5.4 *	22	43.7±5.1
3-9 days	55	36.8±2.95	21	35.8±3.65
12-21 days	44	35.3±3.08	12	32.9±2.78

* Standard deviation of the series.

The temporary anemia found in young rats does not seem to be greater in the jj than in the Jj or JJ animals. However, it may have a hemolytic component and therefore contribute to the jaundice seen during the same period. Table 3 presents hematocrit values at four different intervals during the first 21 days of life.

Hematocrit Values of Adult Rats.—Table 4 presents the average hematocrit values for adult animals of both sexes and different genetic types. It does appear, as was reported by Gunn, that there may be a slight anemia in the affected animals.

Evidence that this slight anemia is not indicative of hemolysis as the cause of the jaundice is presented in Table 5. There is no inverse relationship between hematocrit and degree of bilirubinemia, so far as average values are appropriate in the analysis of the situation.

TABLE 4.—*Hematocrit Values of Adult Rats*

	Jaundiced		Nonjaundiced		
Genotype and Sex	jj Male	jj Female	Jj Male	Jj Female	JJ Female
No. of rats	14	14	19	21	13
Hematocrit, %	40.4	45.9	52.6	53.2	52.7
Standard deviation *	2.7	1.7	3.4	2.5	1.6

* Standard deviation of the series.

The rats were at least 3 months old and had not been bled in over one month. Jaundiced females had had no successful pregnancies. Nonjaundiced females had had no pregnancies in over one month.

TABLE 5.—*Hematocrit Values in jj Rats Grouped According to Degree of Jaundice*

	Serum Bilirubin Under 10 Mg/100 Ml.		Serum Bilirubin Over 10 Mg/100 Ml.	
	Male	Female	Male	Female
No. of rats	8	8	6	6
Hematocrit, %	49.7	45.7	49.1	46.0

TABLE 6.—*Unusual Fluctuations of Indirect Serum Bilirubin (Mg/100 Ml.) and Hematocrit Values in Three Female Jaundiced Adult Rats*

	Rat 1		Rat 2		Rat 3	
Day	Hct., %	Bilirubin, (Mg/100 Ml.)	Hct., %	Bilirubin, (Mg/100 Ml.)	Hct., %	Bilirubin, (Mg/100 Ml.)
0	38	19.5	35	26.0	35	23.8
1 week later	45	7.2	37	11.7	38	17.2
2 weeks later					46	9.7

Individual instances were encountered of a transitory, severer anemia, and a parallel intensification of jaundice was observed. Respiratory infection was common in the colony at the time and may have played a role. Table 6 provides data on three such occurrences.

Kernicterus.—Kernicterus in this strain of rats, as in humans, occurs with rare but important exceptions only in the young. Both the frequency and the severity of the nervous system abnormalities and the intensity of nuclear staining are related to the degree of hyperbilirubinemia. Some animals, as is the case with some humans, are better able than others to withstand severe

TABLE 7.—*Terminal* * *Indirect Serum Bilirubin Values in Jaundiced (jj) Rats with Kernicterus*

Litter	Age in Days	No. Prior Bleedings	Hematocrit, %	Indirect Bilirubin Mg/100 Ml.	Pulmonary Hemorrhage †	Comment
34	4	0	—	6.5	0	Pneumonia in siblings; brief heat prostration
128	5	0	40	20.0	+	
141	6	1	36	12.0	+	
92	7	0	38	13.0	+	
32	7	0	—	13.5	+	S. B. on day 6; died day 7
74	8	0	56	26.0	0	Classical signs of kernicterus
74	8	0	51	22.0	—	Missing 2 hr. after bleeding
74	10	1	36	15.5	0	Classical signs of kernicterus
110	10	0	—	17.0	+	
128	11	0	56	19.5	+	
70	12	0	31	18.0	0	
32	13	3	22	14.5	0	
70	14	0	40	16.0	0	
75	14	0	43	13.5	0	
8	15	0	—	20.5	+	
93	15	2	51	18.5	0	Lungs stained yellow at periphery
72	16	0	45	24.5	0	
50	17	2	31	10.0	0	Much blood taken
95	17	1	46	22.0	0	
94	17	1	44	16.5	0	
111	19	1	44	15.0	0	
94	19	1	39	14.0	0	Resolving pneumonia
87	19	0	54	15.0	0	
110	21	1	45	22.5	+	
43	22	2	41	20.5	0	
8	23	0	—	16.5	+	
95	25	1	50	13.5	0	
50	26	3	38	10.0	—	Signs of kernicterus for 13 days; found half eaten by mother on day 27; much blood taken days 14 & 26.

* Blood was drawn when death appeared inevitable and in most instances the animal was then killed.

† In the lungs examined microscopically the pulmonary lesion which in the gross could not be designated definitely as hemorrhage as opposed to hemorrhagic penumonia was always found to be primarily one of hemorrhage. In those specimens in which microscopic examination was not performed, the lesion was presumed to be one of pulmonary hemorrhage. In some instances infection was probably also present or even primary.

TABLE 8.—*Terminal* Indirect Serum Bilirubin Values in Jaundiced (jj) Rats Without Distinct Localized Staining of the Brain at Postmortem Examination*

Litter	Age in Days	No. Prior Bleedings	Hematocrit	Indirect Bilirubin Mg/100 Ml.	Pulmonary Hemorrhage †	Comment
112	1	0	42	5.5	+	
30	2	0	43	5.5	0	
96	3	0	36	8.2	+	Birth trauma, hemoperitoneum
111	4	0	40	10.0	+	‡
128	5	0	45	15.0	+	‡
126	7	0	30	17.5	+++	‡
89	12	2	—	8.6	+	
75	14	0	43	13.5	0	Jj sibling sick, but recovered
33	15	3	—	12.4	+	

* Blood was drawn when death appeared inevitable. In most instances the animal was then killed.
† This is a gross diagnosis. Microscopic examination of the lungs has not been completed.
‡ Microscopic examination of these brains has not been completed. Grossly there was equivocal yellow staining of the basal ganglia.

hyperbilirubinemia. Graph 1 and Tables 7, 8, and 9 apply to these statements.

In the first few days of life, jaundiced animals are usually as large and strong as nonjaundiced. Those killed under age 2 days were found to have brains which were without localized yellow stain and which were histologically normal. A faint generalized yellow stain was present, however. One exception to this statement was encountered in the appearance of yellow pigmentation in the thalamus and hippocampus of the brain of a jj rat only 4-5 hours old (see section on postmortem findings). This rat had been killed because of its poor condition following a traumatic birth. Clinical jaundice was already present but no bilirubin measurement was made. The finding of pigmentation in this animal will require us, for a future project, to examine the brains of rats born to jaundiced parents and delivered by cesarean section or killed at the moment of birth.

The earliest age at which we have seen obvious gross localized pigmentation of the brain in untreated jj rats is four days. At such an age kernicterus is found almost always to have been potentiated by an infection or stress of some sort. Tables 7, 8, and 9 relate the incidence of kernicterus to age, infection, serum bilirubin level, and blood loss. Graph 1 compares the pattern of bilirubin levels in rats which survived with that of rats which died with kernicterus. It is obvious that kernicterus and death are associated with higher bilirubin levels. A clinical diagnosis of kernicterus is difficult to make before 10 days of age, by which time the normal rats are mature enough to walk fairly well. Neuromotor ataxia and incoordination appear, followed by weight loss, varying degrees of hypotonia, and purposeless hyperactivity. Death uniformly follows if weight loss is severe, accelerated no doubt by an inability to suck. It is often preceded by periods of athetoid writhings or episodes of opisthotonus, and occasionally by clonic convulsions. The greatest incidence of death is in the third week, detectable illness having lasted 5 to 10 days.

Morbidity and mortality statistics are difficult to interpret, because our colony was plagued by intercurrent infections. Mortality during the first month of life among 135 jaundiced untreated rats born between June, 1956, and November, 1957, fluctuated widely, the range being between 25% and 80%.‖ The incidence of classical signs of kernicterus or of localized yellow staining at postmortem examination is relatively constant, however, regardless of intercurrent infection. The average incidence was 58%. Of 52 jj animals which survived, 26 had no detectable nervous abnormalities.

‖ These figures were obtained by considering three successive time periods during which untreated jj rats were born. These periods represent times of moderate, little, and much intercurrent illness, respectively.

TABLE 9.—*Peak Indirect Serum Bilirubin Values in Jaundiced (jj) Rats Which Survived to Adulthood, Some With and Some Without Clinical Signs of Kernicterus*

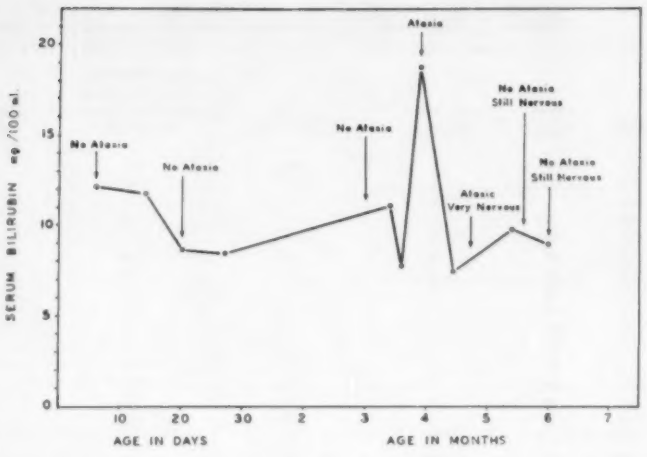
Litter	Age in Days	No. Prior Bleedings	Hematocrit, %	Peak * Indirect Bilirubin During 1st Month of Life Mg/100 Ml.	Intercurrent Infection	Signs of Neuromotor Disability
111	4	0	39	10.5	+	2+
78	6	0	33	12.2	+	0
49	7	1	30	9.1	0	0
46	9	1	—	9.7	+	0
46	13	2	37	13.7	+	4+
60	13	2	30	13.5	0	0
63	13	2	36	12.5	+	3+
62	14	2	35	14.1	+	3+
78	14	1	32	13.4	+	0
89	14	1	37	9.7	+	1—
67	14	1	29	12.5	0	1—
67	14	1	37	8.9	0	0
104	14	1	34	16.5	+	1—
104	14	1	40	15.6	+	1+
104	14	1	38	15.7	+	1+
70	15	0	34	13.8	0	4+
68	15	0	35	9.8	0	2+
68	15	0	33	10.0	0	2+
57	15	2	29	10.5	0	0
77	15	1	32	12.2	+	0
79	15	0	40	10.8	+	1+
94	15	0	31	10.4	+	1+
71	16	0	33	10.0	0	4+
72	16	0	35	12.3	0	4+
72	16	0	36	11.2	0	3+
72	16	6	34	11.9	0	3+
65	16	2	28	12.0	0	0
69	16	0	30	11.8	0	1+
128	18	0	30	9.3	0	0
110	20	0	37	13.0	+	2+
110	20	0	32	12.6	+	0
125	20	0	35	14.8	0	0
125	20	0	36	15.0	0	1+
125	20	0	36	14.4	0	0
67	21	2	36	11.8	0	2+
G	21	0	—	14.5	0	3+
90	21	2	45	14.5	+	4+
63	22	3	31	12.5	+	0
79B	22	2	38	11.3	0	1+
67	23	3	36	10.3	0	1—
66	23	2	35	9.8	+	2+

* This represents the peak value measured, but not necessarily the peak value, since relatively few determinations are possible in such small animals.

Among jaundiced animals which survive there is found a decreased resistance to infection, starvation, heat and cold. Varying degrees of growth stunting and infertility occur, especially among females. The degree of growth stunting was not necessarily proportionate to the degree of nervous system disability in these animals.

Development of Kernicterus After the Newborn Period.—We believe that neural damage, when it occurs in association with hyperbilirubinemia, almost always occurs during the first month of life. However, the severity of damage cannot necessarily be predicted from the symptoms manifested during this time. It is likely that in the rats, as in humans, the nervous signs are modified by maturation of the central nervous system.

An animal in which no evidence of nervous system damage has been seen during the first three months, ordinarily remains without clinical evidence of such damage for the rest of its life. An interesting exception was encountered, however. One animal whose bilirubin level was being followed serially and in which no nervous system abnormality had ever been noted,



Graph 2.—Course of indirect serum bilirubin in a jj (jaundiced) animal whose signs of nerve cell damage did not appear until it was 4 months old, during a transitory episode of intensified jaundice.

developed motor difficulties early in the fourth month of life in association with a sudden and unexplained rise in bilirubin, possibly related to an unobserved infection (Graph 2). The bilirubin elevation was transitory but the ataxia persisted for four weeks, and extreme nervousness was still present at age 6 months.

Other examples of fluctuations in degree of bilirubinemia in adult animals were encountered as mentioned previously, without the parallel development of central nervous system damage. These adult animals withstood bilirubin levels far in excess of those which are fatal in rats under a month of age. The latter rarely survive levels in excess of 15 mg/100 ml.

Postmortem Findings.—Figures 1 and 2 are photographs of the brain of a jaundiced animal whose clinical course had been typical of kernicterus. There is yellow pigmentation of the inferior colliculus and the basal ganglia. Areas frequently seen to be so stained include the globus pallidus, putamen, caudate nucleus, nuclei of the thalamus, olfactory bulb and tract, olfactory striae, hippocampus, nuclei of the eighth nerve, inferior colliculus, cerebellum, gray matter of the spinal cord, and sometimes the cerebral cortex. The color remained yellow in 10% formaldehyde and faded in a few weeks at room temperature. The color persisted for a longer period if the material was kept in a refrigerator. In frozen brains it persisted for at least four months.

The microscopic findings are also typical of kernicterus as it has been described in human infants. Figure 3 is a photograph of a frozen section. The reproduction is sufficiently clear to show yellow pigment within nerve cells. Details of cell structure are better seen in Figures 4 and 5.

Microscopic examination was performed on routine hematoxylin-and-eosin-stained sections of paraffin-embedded material in 54 cases, including controls. Frozen sections were made of all brains still showing definite gross pigmentation when received in the pathology laboratory. Frozen sections were 20μ to 30μ thick and were examined both unstained and after staining with methylene blue and scarlet red.

In thick frozen sections, the abundant supply of blood capillaries was obvious in all areas showing bilirubin staining. Thus the attribution of a differential staining to local anoxia secondary to poor vascularization appears unlikely.

Bright yellow granules were found within the cytoplasm of a variable number of ganglion cells in all cases showing gross pigmentation and in a few cases where gross pigmentation had faded. The earliest damage with pigmentation was found in a 4- or 5-hour-old jj rat (untreated). Only an occasional cell appeared shrunken and granu-

Figure 1

Fig. 1.—Localized staining of the surface of the inferior colliculus as seen in a photograph of the fresh brain of a jj rat whose progressive symptoms of kernicterus had been first noted on Day 11. This rat was given a subcutaneous injection of 0.7 mg. of bilirubin on Day 17.. It died on Day 18, after many hours of extreme lethargy interrupted by tonic and clonic convulsions. The total serum bilirubin just before death was 17.5 mg/100 ml., almost all of which was of the indirect reacting type.

Figure 2

Fig. 2.—Photograph of the cut surface of the fresh brain specimen described under Figure 1 showing localized staining of the inferior colliculus.

Figure 3

Fig. 3—Photomicrograph of an unstained frozen section showing yellow pigment within ganglion cells of the basal ganglia of the jj rat described under Figure 1.

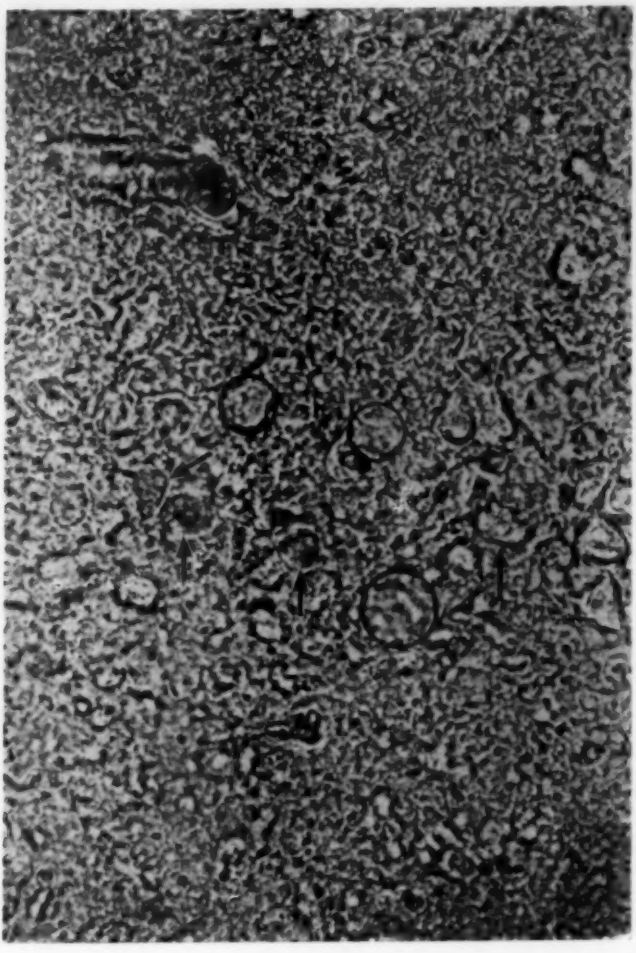


Fig. 4.—Unstained frozen section of hippocampus of an 11-day-old jj rat with severe kericterus. Intact neurons and their nuclei are barely visible and have faint outlines (black circles). Damaged cells stand out with bright cytoplasm and sharp dark edges, and some cells show a finely vacuolated appearance (black arrows); all these cells had intense yellow staining. The small round cells are glial cells; some are also vacuolated and contain pigment. This animal received 100 mg/kg/day of a long-acting sulfonamide drug on Days 9 and 10 (reduced about 8% from mag. ×750).

lar and contained a few pale yellow droplets. These cells were found in the hippocampus and in the thalamus. Usually the alterations are best observed at the end of the first week and thereafter. Except for variation in extent and severity, the changes are qualitatively similar in animals with spontaneous kernicterus and in those medicated as described in a later section. No pathological alterations were observed in Jj and normal rats of various ages, with or without treatment with sulfonamides. No pathological changes were seen in jj animals showing no clinical signs of kernicterus or gross postmortem evidence of staining.

In the altered cells, the first change, apparently always associated with early and minimal bilirubin impregnation, was a tendency to take a spherical shape. The cytoplasm became granular, and the cell membrane was easily made out. All these cells stood out among the other normal cells. The nucleus tended to lose its contours, become peripheral in position and later undergo pyknosis or, less commonly, karyolysis. The cytoplasmic granules appeared coarser and irregular in size, and the cell shrank with final lysis and release of pigmented granular material. A minimal glial reaction was elicited, and some scav-

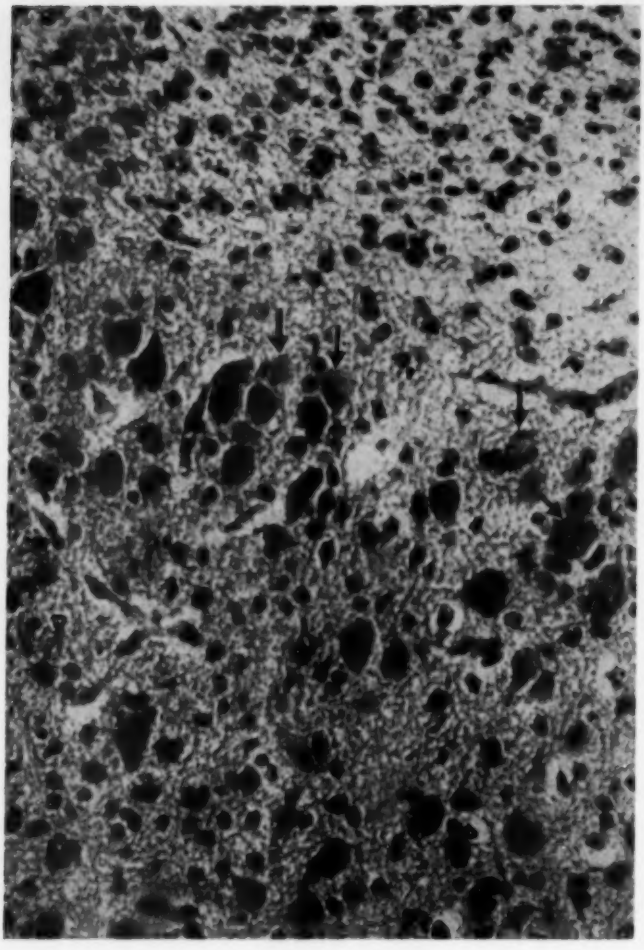


Fig. 5. — Hematoxylin and eosin stain of hippocampus of a 12-day-old jj rat with kernicterus. The normal pattern with regularly spaced neurons is disrupted, and there is an increase in small glial cells with satellitosis. The very dark cells represent an artefactitious change. Damaged cells undergo lysis (arrows). This animal received sodium sulfisoxazole 500 mg/kg/day (reduced about 8% from mag. ×750).

enger cells containing bilirubin pigment appeared. In spite of careful search, we could not find a ganglion cell which was definitely icteric and at the same time normal in its other characteristics. It is possible, however, because of the technical difficulties involved, that a minimal degree of staining was overlooked. Frequently, normal cells surrounded badly damaged cells. In paraffin-embedded material, the altered cells appeared vacuolated with peripheral nuclei and, at a later stage, shrunken, with pyknotic nuclei. Bilirubin pigment was found only exceptionally in embedded material. It seems that the earliest changes accompanying bilirubin staining may well be completely missed in these sections. It was also difficult to differentiate the above lesions from the "normal" artefacts of shrinkage, basophilia, or pallor of ganglion cells observed also in controls. With training, it became possible to diagnose the acute kernicterus cases on paraffin sections and to obtain consistent readings on blind tests. Although we cannot completely exclude the possibility of mild changes occurring before bilirubin staining, this seems unlikely since, in kernicteric rats, the ganglion cells appeared either normal or icteric. In animals in the fourth week of life and older,

ganglion cell loss was evident and this was the only demonstrable alteration observed in adults with a clinical history of kernicterus. Studies of myelinization and microglial tissue are in progress.

Lesions observed in other organs include, in the acute stage, massive intrapulmonary hemorrhage, a quite characteristic finding, and mild fatty metamorphosis of the liver.

A deposition of an orange-yellow substance at the tip of the single pyramid of the kidney was noted in all jaundiced rats which died or were killed beyond one month of age (regardless of the presence or absence of nervous system damage). This was not noted in animals under approximately 3 weeks of age. Microscopic examination revealed crystals of bilirubin in the interstitial tissue at this site.

Factors Intensifying Kernicterus

The Sulfonamides.—In 1956, Silverman et al.[40] reported an epidemic of kernicterus among premature infants treated with sulfisoxazole diethanolamine (Gantrisin).

We have been able to reproduce this finding in young, jaundiced rats with sodium sulfadiazine,¶ sodium sulfisoxazole,¶ and sulfisoxazole diethanolamine ¶ (Table 10 and Graph 3). In contrast with normal young rats, the jaundiced strain is easily killed by these drugs. Table 11 shows that sulfadiazine blood levels are about the same in jaundiced as in nonjaundiced rats receiving the same dosage of drug.

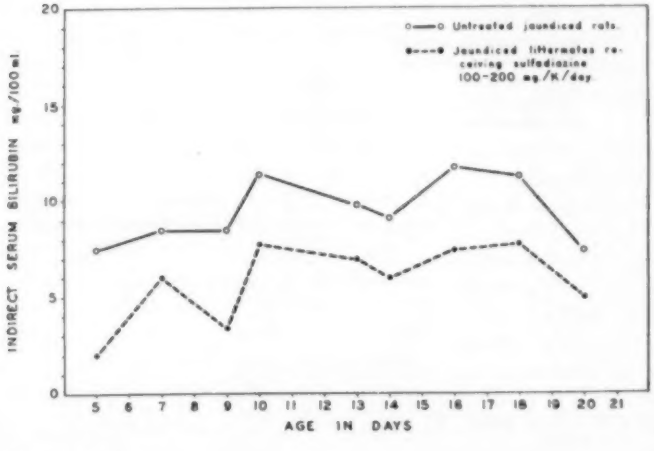
Of special interest is the fact that the serum bilirubin level is reduced by the injection of these drugs (Graph 3), while at the same time it is noted at autopsy that the yellow staining is especially intense. This is true not only of the gray matter of the central nervous system, but of depot fat and connective tissue. In five rats which died within 48 hours after injections of

¶ Obtained through the courtesy of Hoffmann-La Roche.

TABLE 10.—*Effect of the Sulfonamide Drugs on Mortality in the Gunn Colony of Rats*

	jj Rats Treated with a Drug		jj Litter Mate Controls (No Drug)		Jj or JJ Litter Mates Treated with the Same or Higher Drug Dosage	
	Lived	Died	Lived	Died	Lived	Died
Sulfix						
Gantrisin	0	12	6	2	8	0
Sulfadiazine	1	23	9	4	34	0
Totals	1	35	15	6	42	0

The dosages in the jaundiced rats ranged from 100 to 500 mg/kg/day, subcutaneously. The range was the same for the nonjaundiced animals except that three of them received 1,000 mg/kg/day for over a week without apparent ill effect. The mean serum bilirubin in moribund animals given sulfisoxazole or sulfadiazine was 6.9 mg/100 ml. That of those receiving no drug was 12.8 mg/100 ml.


o——o Untreated jaundiced rats.
•- - -• Jaundiced littermates receiving sulfadiazine 100-200 mg./K/day
INDIRECT SERUM BILIRUBIN mg/100 ml
AGE IN DAYS
0
5
10
15
20
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Graph 3.—Effect of sodium sulfadiazine 100-200 mg/kg/day on indirect serum bilirubin levels in genetically jaundiced rats. The upper curve represents the course of serum bilirubin in nine control rats given no drug; four of these rats died. The lower curve represents the course of serum bilirubin in 16 rats given sulfadiazine, of which all but 1 died and had kernicterus at postmortem examination. The mean depression of serum bilirubin was 30%. P=0.001.

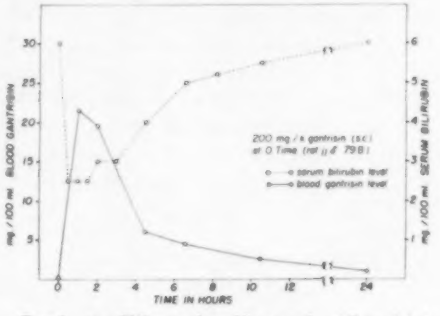
TABLE 11.—*Comparison of Free Sulfadiazine Levels in Jaundiced (jj) and Nonjaundiced (Jj) Rats*

Age	Dosage/Kg. (Mg/Kg/Day)	Duration, Days	Hours After Last Dose	Free Sulf. Level (Mg/100 Ml.) jj	Free Sulf. Level (Mg/100 Ml.) Jj	Blood Urea Nitrogen (Mg/100 Ml.) jj	Blood Urea Nitrogen (Mg/100 Ml.) Jj
2 weeks	100	10	2½	11.0	10.5	27.0	
3 weeks	100	14	4-6	9.5	7.5		
Adult	200	2	4-6	10.0	10.5	19.0	26.7
				8.6	9.8	25.0	24.5
				9.6	12.3	14.5	25.6

a long-acting sulfonamide preparation,# intense staining of the intestine distal to the ampulla of Vater was observed at post mortem. Microscopic examination revealed crystalline and amorphous deposits of a pigment resembling bilirubin in the lamina propria of the intestinal mucosa.

The serum bilirubin levels of adult jaundiced rats are also lowered by these sulfonamide preparations, and the skin of the ears and feet appear more yellow, but the nervous system is uninjured even after 2 weeks of medication. The decline in serum bilirubin concentration is rapid and prompt, and bilirubin levels are inversely related to levels of sulfonamide in the blood (Graphs 4 and 5).

Supplemental Bilirubin.—Subcutaneous injections of bilirubin in amounts which do not kill normal young rats or cause

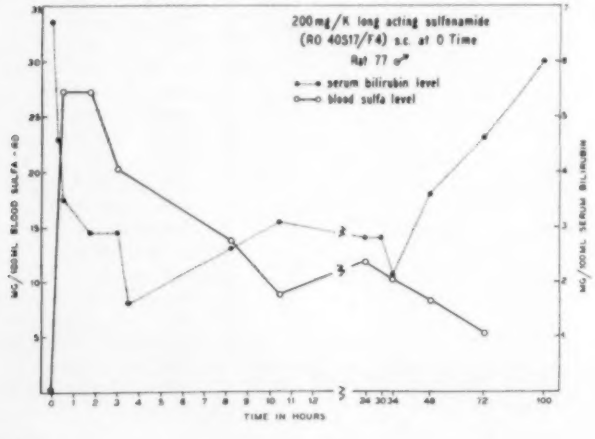

200 mg./k gantrisin (s.c.)
at 0 Time (rat jj d' 79 B)
serum bilirubin level
blood gantrisin level
mg./100 ml. BLOOD GANTRISIN
mg./100 ml. SERUM BILIRUBIN
TIME IN HOURS

Graph. 4.—Effect of sulfisoxazole (Gantrisin) on serum bilirubin levels.

detectable brain damage increase the severity of neurotoxic signs and the degree of central nervous system staining in the jaundiced animals. However, the response to a particular dose of bilirubin in a particular animal is difficult to predict.

Infections.—No clear-cut relation of kernicterus to infections has been found, but in individual instances increased intensity of localized brain pigmentation and early

A parenteral preparation, No. RO 40517/F4, marketed as Madribon, obtained through the courtesy of Hoffmann-La Roche.



Graph 5. — Effect of long-acting sulfonamide on serum bilirubin levels.

death have been seen in association with severe infection, particularly in animals in which sepsis is suggested by the presence of scattered petechial hemorrhages.

Sodium Glucuronate.—Danoff and coworkers [10] have advocated sodium glucuronate for the control of hyperbilirubinemia in infants and have hypothesized that conjugation occurs with the excretion of direct bilirubin. In rats, we have found a variable response in serum bilirubin levels to 1 to 2 gm/kg/day of sodium glucuronate * injected either intraperitoneally or subcutaneously. Usually there was a fall, which at times exceeded 50%. However, the incidence of kernicterus was not reduced. Of 18 young jaundiced rats given 1 gm/kg/day of the glucuronate over periods ranging from 2 to 14 days, 13 developed kernicterus. Nine of these died, and the kernicterus was proved at postmortem examination. Substantial lowering of the serum bilirubin level did not postpone the onset of signs of nervous system damage. In five animals from which biopsy specimens were taken before and after injection, increased staining of fat of the groin and back was noted concomitantly with the fall in serum bilirubin concentration. Lowering of serum bilirubin levels in adult jaundiced animals was much more difficult to achieve. Even intravenous injection of as much as 3 gm/kg. of glucuronate over a three-hour period lowered the bilirubin in only one of two rats. No kernicterus was produced in these adult rats.

Hypoxia.—The higher incidence of kernicterus in premature as compared with mature infants has been related by some to their greater tendency to episodes of hypoxia. We sought evidence that such episodes might prove intolerable to the jaundiced rats, but none was found.

From preliminary observations, the tolerance of normal rats to an atmosphere of nitrogen on each day of life for the first 7 days had been established. Subsequently, jaundiced and nonjaundiced rats were exposed daily to a period of total anoxia calculated to kill some but not all the animals. The rapid maturation of the rats required that this period be lessened each day. Table 12 shows the results. In summary, it is seen that 98 of 127 nonjaundiced animals survived and 44 of 49 jaundiced animals survived. Furthermore, there was no apparent increase in incidence or severity of kernicterus among the jaundiced rats so exposed. Whether continuous exposure to moderate anoxia would have different results is not known.

* Supplied by the Vitarine Company through the courtesy of Mr. Harold Neumark.

Comment

The similarity between rats of the Gunn strain and the patients described by Crigler and Najjar,[9] Childs and Najjar,[7] and Rosenthal et al.[35] is striking. The defect in glucuronyl transferase activity found in the liver of a similarly affected adult by Arias and London [1] is almost surely present in these children. Like the rats, the children vary in their ability to withstand hyperbilirubinemia. Rosenthal's patient, who first developed neurologic signs when 3 years old, behaved similarly to our rat which was well until 4 months of age.

The rats provided a tool for studying some of the puzzles of kernicterus and of jaundice in human infants. The above observations lend support to the idea that bilirubin is both the toxic and the staining agent. However, the variations in susceptibility, the clearly greater resistance of more mature animals, and the seeming potentiation of bilirubin toxicity by sulfonamide drugs leave many questions still to be answered. We know very little about what else besides hyperbilirubinemia is required before kernicterus will develop. That membrane permeability and relative immaturity of the "blood-brain barrier" play a role in the increased susceptibility of the young appears likely. Of equal importance may be factors which interfere with or limit the ability of the infant to maintain bilirubin in a bound state within the blood stream prior to its excretion. The observation of Odell that sulfonamides promote the dialysis of bilirubin from serum supports such

TABLE 12.—*Tolerance of Young Jaundiced and Nonjaundiced Rats to Anoxia*

Day of Life	Type of Rat	Minutes of Exposure to Anoxia (Atmosphere of 100% N)											
		40	35	33	30	27	25	23	20	17	15	13	10
1	Nonjaundiced	4/16	10/11										
	Jaundiced	0/4	4/4										
2	Nonjaundiced		0/9	5/5	17/17								
	Jaundiced				8/8								
3	Nonjaundiced				9/11	8/8	14/14						
	Jaundiced					4/4	5/5						
4	Nonjaundiced						10/11						
	Jaundiced						4/4						
5	Nonjaundiced							1/3		4/5			
	Jaundiced							4/4		3/3			
6	Nonjaundiced								1/1			8/9	
	Jaundiced								4/4			0/1	
7	Nonjaundiced										1/1		6/6
	Jaundiced										4/4		4/4
Totals	Nonjaundiced			98/127	= 77% survival								
	Jaundiced			44/49	= 90% survival								

Upper figure of each fraction = number surviving.
Lower figure of each fraction = number exposed.

a hypothesis.[34] With regard to the Gunn rats, it is also possible that there are other defects which predispose them to kernicterus.

The prolonged period of increased hyperbilirubinemia in jj rats during the first month of life is puzzling. Brown and Zuelzer[5] have found the livers of newborn and fetal guinea pigs to have an impairment in UDPG dehydrogenase activity as well as that of glucuronyl transferase. Lathe and Walker[28] have demonstrated an inhibitory effect of human pregnancy serum on bilirubin conjugation. It is possible that such factors of immaturity and inhibition play a role in the rapid postnatal rise in serum bilirubin found in these rats as well as in the slower further rise which occurs after the second day, continuing usually until the third week of life. It could be that there is a hemolytic element in the anemia which develops during the same period. It could also be that some alternate route of bilirubin metabolism, not utilized to an appreciable degree in nonjaundiced rats, develops during this time. Since jaundiced adults of this species have fairly constant levels of bilirubin in their sera, their excretory mechanism must be adequate to rid the body of its daily bilirubin load. The marked in vitro depression in the ability of their livers to form bilirubin glucuronide by way of glucuronyl transferase makes it reasonable to postulate that an additional pathway of excretion exists, operating perhaps at a threshold of 5 to 10 mg/100 ml. of serum bilirubin.

The absence of jaundice in jj rats at birth, even when the mother has elevated levels, is unexplained. One would expect

bilirubin to pass the three-layered placenta of the rat. At least, such passage from erythroblastotic human infants to the nonjaundiced mother makes an attractive, though unproved, explanation for the low levels found in the infant at birth. In the jj mother rat, whose fetuses are also jj in type, it is hard to imagine what happens to the bilirubin. More facts are needed before speculation would be profitable to the reader.

Summary

The natural history of kernicterus in rats with an inherited defect in liver glucuronyl transferase is reported.

These rats develop kernicterus which is identical with that seen in human beings. It appears to be the only example of kernicterus in animals which fulfills the following criteria: (1) distinctive evidence of central nervous system abnormality during life in jaundiced subjects; (2) canary yellow staining of nuclear masses of the central nervous system clearly visible in gross specimens; (3) persistence of the stain when the tissue is fixed in formalin; (4) presence of pigment within ganglion cells; (5) evidence of degeneration of nerve cells in sections examined microscopically.

A paradoxical lowering of serum bilirubin and intensification of nervous signs and nuclear staining is produced by treatment of the animals with sulfonamides. A rational hypothesis, also suggested by Odell, is that this effect is the result of a competition between bilirubin and the sulfonamides for binding sites on the serum albumin.

Daily exposures to an atmosphere of nitrogen for periods sufficient to kill 25% of control newborn rats does not lead to any greater mortality among jaundiced rats.

Newborn rats with the inherited defect, even when born to bilirubinemic mothers, have levels of bilirubin which are low at the moment of birth but rise rapidly in the first hours of life.

Bilirubin appears from these observations to be toxic, but unknown factors, drug treatment, and maturation of the animal modify its action.

These rats should provide a useful tool for studying ways to detoxify bilirubin, to hasten its excretion, or to stabilize it in a bound state within the vascular compartment.

Technical assistance was given by Mr. Curtis Washington.

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REFERENCES

1. Arias, I. M., and London, I. M.: Bilirubin Glucuronide Formation in Vitro; Demonstration of a Defect in Gilbert's Disease, Science 126: 563, 1957.

2. Billing, B. H., and Lathe, G. H.: The Excretion of Bilirubin as an Ester Glucuronide, Giving the Direct van den Bergh Reaction, Biochem. J. 63:6P, 1956.

3. Billing, B. H.; Cole, P. G., and Lathe, G. H.: The Excretion of Bilirubin as as Diglucuronide Giving the Direct van den Bergh Reaction, Biochem, J. 65:774, 1957.

4. Bratton, A. C., and Marshall, E. K.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. 128:537, 1939.

5. Brown, A. K., and Zuelzer, W. W.: Mechanism and Significance of Hyperbilirubinemia in the Newborn with Reference to Kernicterus, read before the 11th Annual Meeting, American Academy for Cerebral Palsy, New Orleans, Nov., 1957.

6. Carbone, J. V., and Grodsky, G. M.: Constitutional Nonhemolytic Hyperbilirubinemia in the Rat: Defect of Bilirubin Conjugation, Proc. Soc. Exper. Biol. & Med. 94:461, 1957.

7. Childs, B., and Najjar, V. A.: Familial Nonhemolytic Jaundice with Kernicterus: a Report of 2 Cases Without Neurologic Damage, Pediatrics 18:369, 1956.

8. Cole, P. G.; Lathe, G. H., and Billing, B. H.: Separation of the Bile Pigments of Serum, Bile and Urine, Biochem. J. 57:514, 1954.

9. Crigler, J. F., and Najjar, V. A.: Congenital Familial Nonhemolytic Jaundice with Kernicterus, Pediatrics 10:169, 1952.

10. Danoff, S.; Boyer, A., and Holt, L. E., Jr.: Observations on the Control of Bilirubinemia, Program of the 28th Annual Meeting of the Society for Pediatric Research, Atlantic City, May 6-7, 1958, Abstract 13, p. 11.

11. Davis, B.: The Binding of Sulfonamide Drugs by Plasma Proteins: A Factor in Determining the Distribution of Drugs in the Body, J. Clin. Invest. 22:753, 1943.

12. Day, R. L.: In Vitro Effect of Bilirubin on Brain Respiration, presented at the 25th Anniversary Celebration of Columbia-Presbyterian Medical Center, Babies Hospital, New York, Oct., 1953.

13. Day, R. L.: Inhibition of Brain Respiration in Vitro by Bilirubin: Reversal of Inhibition by Various Means, Proc. Soc. Exper. Biol. & Med. 85:261, 1954.

14. Day, R.: Kernicterus; Further Observations on the Toxicity of Heme Pigments, Pediatrics 17: 925, 1956.

15. Day, R. L., and Johnson, L.: Kernicterus, to be published.

16. Dameshek, W., and Singer, K.: Familial Nonhemolytic Jaundice, Arch. Int. Med. 67:259, 1941.

17. Dereymaeker, A.: L'ictere nucléaire du nouveau-né, Bruxelles, Editions Arscia, 1949.

18. Dutton, G. J., and Storey, I. D. E.: Uridine Compounds in Gluronic Acid and Metabolism: The Isolation and Structure of Uridine-Diphosphate-Glucuronic Acid, Biochem. J. 59:279, 1955.

19. Eyquem, A.: L'atteinte du système nerveux central chez les jeunes animaux présentant une maladie hémolytique expérimentale, Compt. rend. Soc. biol. 142:485, 1948.

20. Eyquem, A.: L'ictère nucléaire expérimental, Acta neurol. et psychiat. belg. 49:965, 1949.

21. Ernster, L.; Herlin, L., and Zetterström, R.: Experimental Studies on the Pathogenesis of Kernicterus, Pediatrics 20:647, 1957.

22. Gunn, C. K.: Hereditary Acholuric Jaundice in a New Mutant Strain of Rats, J. Hered. 29:137, 1938.

23. Gunn, C. K.: Hereditary Acholuric Jaundice in the Rat, Canad. M. A. J. 50:230, 1944.

24. Küster, F., and Krings, H.: Die Bedeutung des Bilirubins für die Pathogenese des Hirnschadens bei der Erythroblastosis fetalis, Ztschr. Kinderh. 67:503, 1950.

25. Karunairatnam, M. C.; Kerr, L. M. H., and Levvy, G. A.: The Glucuronide-Synthesizing System in the Mouse, and Its Relationship to B-Glucuronidase, Biochem. J. 45:496, 1949.

26. Lathe, G. H.: The Chemical Pathology of Bile Pigments: Part I. The Plasma Bile Pigments, Biochemical Society Symposia, No. 12, London, Cambridge University Press, 1954, p. 34.

27. Lathe, G. H., and Walker, M.: An Enzyme Defect in Human Neonatal Jaundice and in Gunn's Strain of Jaundiced Rats, Biochem. J. 67: 9P, 1957.

28. Lathe, G. H., and Walker, M.: The Inhibitory Effect of Human Pregnancy Serum on Bilirubin Conjugation, to be published.

29. Levvy, G. A.: Glucuronide Metabolism with Special Reference to the Steroid Hormones, Vitamins & Hormones 14:267, 1956.

30. Lipschitz, W. L., and Bueding, E.: Mechanism of the Biological Formation of Conjugated Glucuronic Acids, J. Biol. Chem. 129:333, 1939.

31. Malloy, H. T., and Lowenstein, L.: Hereditary Jaundice in the Rat, Canad. M. A. J. 42:122, 1940.

32. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. 119:481, 1937.

33. Meulengracht, E.: Review of Chronic Intermittent Juvenile Jaundice, Quart. J. Med. 16:83, 1947.

34. Odell, G. B.: In Vitro Studies of the Effect of Sulfonamides on Bilirubin, Program of the 28th Annual Meeting of the Society for Pediatric Research, Atlantic City, May 6-7, 1958, Abstract 156, p. 147.

35. Rosenthal, I. M.; Zimmerman, H. J., and Hardy, N.: Congenital Nonhemolytic Jaundice with Disease of the Central Nervous System, Pediatrics 18:378, 1956.

36. Schmid, R.: Bilirubin Glucuronide, the Direct Reacting Bilirubin, in Serum, Bile and Urine, Science 124:76, 1956.

37. Schmid, R.; Hammaker, L., and Axelrod, J.: The Enzymatic Formation of Bilirubin Glucuronide, Arch. Biochem. 70:285, 1957.

38. Schmid, R.; Axelrod, J., and Hammaker, L.: Congenital Defects in Bilirubin Metabolism, American Society of Clinical Investigation, May, 1957, abstract, p. 63.

39. Schmorl, G.: Zur Kenntnis des Ikterus neonatorum, insbesondere der dabei auftretenden Gehirnveränderungen, Verhandl. deutsch. path. Gesellsch. 15:109-115, 1904.

40. Silverman, W. A.; Andersen, D. H.; Blanc, W. A., and Crozier, D. N.: A Difference in Mortality Rate and Incidence of Kernicterus Among Premature Infants Allotted to Two Prophylactic Antibacterial Regimens, Pediatrics 18:614, 1956.

41. Strominger, J. L.; Kalckar, H. M.; Axelrod, J., and Manvell, E. S.: The Enzymatic Oxidation of Uridine Diphosphate Glucose to Uridine Diphosphate Glucuronic Acid, J. Am. Chem. Soc. 76:6411, 1954.

42. Strominger, J. L.; Maxwell, E. S.; Axelrod, J., and Kalckar, H. M.: The Enzymatic Formation of Uridine Diphosphoglucuronic Acid, J. Biol. Chem. 224:79, 1957.

43. Talafant, E.: Properties and Composition of the Bile Pigment Giving a Direct Diazo Reaction, Nature, London 178:312, 1956.

44. Waters, W. J. W.; Richart, D. A., and Rawson, H. H.: Bilirubin Encephalopathy, Pediatrics 13:319, 1954.

45. Waters, W. J. W., and Britton, H. A.: Bilirubin Encephalopathy: Preliminary Studies Related to Production, Pediatrics 15:45, 1955.

46. Zetterström, R., and Ernster, L.: Bilirubin, an Uncoupler of Oxidative Phosphorylation in Isolated Mitochondria, Nature, London 178:1335, 1956.

An Epidemic of Infectious Hepatitis in the Children's Service of a Psychiatric Hospital

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Administration of γ-globulin to all exposed persons is the only effective means of controlling an epidemic of infectious hepatitis in situations where a group of people live closely together and rigid hygienic standards cannot be maintained. This has been borne out repeatedly in various epidemics since Stokes and Neefe introduced the use of γ-globulin in preventing spread of this disease.[1-7] Our recent experience emphasizes once more that under the above-mentioned circumstances the first occurrence of infectious hepatitis is an indication to give γ-globulin to all contacts.

The epidemic occurred in the Children's Inpatient Service of a psychiatric hospital which provides in- and outpatient treatment for both adults and children. The Children's Service occupies one wing of the hospital building, so at no time did the children come in contact with the adult patients. However, the personnel of the Children's Service mingle with the personnel of the other services, e. g., in conferences or in the dining room. Food for the children, adult patients, and personnel is prepared in one kitchen.

The Children's Service also provides daypatient treatment. The daypatients spend the daytime in the clinic, together with the inpatients, and remain in their own home during the evening and night.

During the epidemic the census on the Children's Inpatient Service amounted to 17 inpatients and 16 daypatients. The nursing staff consisted of 28 members, and there were 17 other professional staff members (doctors, psychologists, social workers, etc.) regularly in close contact with the patients.

On Feb. 24, 1958, a 7-year-old boy became ill with symptoms of malaise, coryza, and low-grade fever. This boy was a severely ill schizophrenic; he was mute and smeared his feces. Three days later he started to pass dark-colored urine. The diagnosis of hepatitis was suspected, and the boy was put in isolation. Liver-function tests confirmed the diagnosis, and five days after the onset of his illness a mild icterus was observed.

On March 14, an aide developed hepatitis; four days later an orderly became ill, and during the next week new cases became manifest almost daily.

Consequently, it was decided not to admit patients to the Children's Inpatient Service and to close the daypatient program. The ward personnel were instructed regarding the mode of transmission in infectious hepatitis. Every new patient among the children was immediately isolated from the other children. Food isolation techniques were introduced; the food was distributed in paper tableware that was discarded after use. One playroom was designated for use by the inpatients only. The other playrooms and the toys therein were thoroughly cleaned and used solely for outpatients. Arrangements were made to administer γ-globulin first to patients and personnel of the Children's Service and then to patients and personnel of the other services and divisions of the hospital.

γ-Globulin was given in a dosage of 0.02 cc. per pound. The Figure illustrates the accumulation of cases among patients and personnel and indicates that among the children the last case became manifest seven

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Course of the epidemic.

days after the passive immunization. Among the nursing personnel the last case developed five days after the passive immunization. Among the other professional personnel no one became ill. Table 1 indicates the disease incidence among the various groups.

In the other services and divisions of the hospital no one developed hepatitis either.

A total of nine children became ill, two of which were daypatients. In most cases the onset of illness was characterized by fever, listlessness, anorexia, and sometimes vomiting. Children who could communicate complained of abdominal pain. Dark-colored urine or clay-colored stools occurred early in the disease among all patients. In one patient the illness started with tonsillitis.

TABLE 1.—*Disease Incidence*

	No. Cases	% (of Whole Group)
Inpatients	7	41
Daypatients	2	12.5
Nursing personnel	9	32
Other professional personnel	0	0

On physical examination, swelling of submandibular and cervical lymph nodes and tenderness or enlargement of the liver were common findings.

In all cases the temperature returned to normal in a few days. Within a period of a week, symptoms of malaise and anorexia had disappeared; by this time four patients had become jaundiced. This jaundice lasted for two to three weeks. In five children the illness had an anicteric course. Among these children were the two daypatients who were treated in their own home by the family physician, and from these cases we do not have laboratory data. The results of the laboratory tests regarding the remaining three anicteric cases are shown in Table 2. In these cases the liver-function tests became normal approximately one month after the onset of the disease. In the patients with icteric hepatitis it was approximately two months before the liver-function tests became normal.

The effectiveness of γ-globulin in controlling the epidemic strongly supports the diagnosis of infectious hepatitis. In order to rule out infectious mononucleosis the heterophil agglutination titer was determined regularly in all patients throughout their illness; however, a diagnostic titer (after differentiation) was never obtained.

Nine members of the nursing personnel became ill. In general, the disease took a similar course as among the children, although the adults were more severely ill than the children; only two patients had anicteric hepatitis. There was no distinct indication of attenuation of the illness among persons who became ill after being immunized, but it can hardly be expected that such a trend would express itself in such a small number of cases.

One nurse became ill five days after receiving γ-globulin, although she had not worked in the hospital since Feb. 28. Prior

TABLE 2.—*Laboratory Data from Three Anicteric Inpatient Cases*

Date	Bilirubin		Thymol Turbidity, Units	Cephalin Flocculation		Serum Transaminase Units
	1 Min., Mg. %	Total, Mg. %		After 24 Hr.	After 48 Hr.	
Patient A						
3-24	0.12	0.35	12.3	4+	4+	
4-2	0.09	0.30	17.7	2+	3+	60
4-14			10.3			95
4-28	0.06	0.12	5.5	Neg.	1+	55
Patient B						
3-29	0	0.12	6.7	Neg.	±	35
4-8			7.3	1+	2+	
4-15			6	2+	3+	61
4-28	0.06	0.12	2.7	2+	3+	36
Patient C						
4-2			11.3	4+	4+	700
4-15	0.18	0.64	7.2	1+	2+	76
4-28	0.12	0.36	3.3	2+	3+	22

to this date she took care of the first hepatitis patient. During the last 10 days of March nine other members of the personnel became ill with vague symptoms, and five of them turned out to have one or two abnormal liver-function tests. These people recovered rapidly, and the diagnosis of hepatitis was not made. Yet several may have had an abortive form of hepatitis.

During the month of April one of the outpatients of the Children's Service developed hepatitis. Relatives of three daypatients also became ill, although these daypatients never showed evidence of having hepatitis. This was also the case of an aide whose daughter developed the disease. Probably in all these cases the contacts had subclinical forms of hepatitis.

In the fourth week of April, 1958, the admission of patients was resumed and the daypatient program was reopened. All new patients and personnel received γ-globulin when they entered the hospital. No one was reimmunized, since previous reports state that one injection of γ-globulin results in long-term protection if the person remains exposed to hepatitis for some time. This is explained by assuming that when the passive immunity wears off the exposed person develops a subclinical infection resulting in active immunization.[5,6,7]

Indeed, up until the present time (October, 1958) no more cases of hepatitis have occurred among our patients or personnel. Because of the nature of their illness our patients remain under our care for a considerable period of time. After inpatient treatment of maximally three months most of them are transferred to the day- or outpatient service. This procedure guarantees a prolonged observation period.

The rapid spread of the illness among the Children's Service is probably connected with the fact that the first patient was a regressed, untidy schizophrenic who, therefore, was an excellent source of fecal contamination. Due to his regression this patient related mainly to the staff, and this would explain why the early cases were limited to the nursing personnel. Unknowingly, they formed a source of contamination for the other patients.

Summary

An epidemic of infectious hepatitis in the Children's Service of a psychiatric hospital is described. This epidemic was effectively controlled with γ-globulin.

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REFERENCES

1. Stokes, J., Jr., and Neefe, J. R.: The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin: Preliminary Note, J. A. M. A. 127:144-145 (Jan. 20) 1945.

2. Gellis, S. S.; Stokes, J., Jr.; Brother, G. M.; Hall, W. M.; Gilmore, H. R.; Beyer, E., and

Morrissey, R. A.: The Use of Human Immune Serum Globulin (Gamma Globulin), in Infectious (Epidemic) Hepatitis in the Mediterranean Theater of Operations: I. Studies on Prophylaxis in 2 Epidemics of Infectious Hepatitis, J. A. M. A. 128:1062-1063 (Aug. 11) 1945.

3. Havens, W. P., and Paul, J. R.: Prevention of Infectious Hepatitis with Gamma Globulin, J. A. M. A. 129:270-272 (Sept. 22) 1945.

4. Gelperin, A., and Hampton, W.: The Ecology of Infectious Hepatitis, Am. J. Pub. Health 45: 1327-1336, 1955.

5. Stokes, J., Jr.; Farquhar, J. A.; Drake, M. E.; Capps, R. B.; Ward, C. S., Jr.; Mills, O., and Kitts, A. W.: Infectious Hepatitis: Length of Protection by Immune Serum Globulin (Gamma Globulin) During Epidemics, J. A. M. A. 147:714-719 (Oct. 20) 1951.

6. Capps, R. B., and Stokes, J., Jr.: Epidemiology of Infectious Hepatitis and Problems of Prevention and Control, J. A. M. A. 149:557-561 (June 7) 1952.

7. Drake, M. E., and Ming, C.: Gamma Globulin in Epidemic Hepatitis: Comparative Value of 2 Dosage Levels, Apparently Near the Minimal Effective Level, J. A. M. A. 155:1302-1305 (Aug. 7) 1954.

Vaginitis in Children

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Prior to the penicillin era most of the reports of vaginitis in children were concerned with the management of gonorrheal vaginitis.[1-3] Since then, gonorrhea has practically disappeared and nonspecific bacterial vaginitis has assumed primary importance.

In this preantibiotic period, estrogen was used widely in the treatment of vaginitis in children. The work of Robert Lewis,[1] in 1933, pioneered this therapeutic approach. Lewis and others[2,4] felt that vaginitis in children was due to an exaggeration of the normal hypoestrogenism of childhood, which in turn produced an atrophy of the vaginal mucosa. Estrogen administration could increase the cellular depth of the vaginal epithelial layer, and this artificially hypertrophied surface acted as a barrier to the invasion of bacteria. Gonorrheal vaginitis was treated therefore with local or systemic estrogens.

In the current reports of preadolescent vaginitis, most authors stress the importance of general health measures, the presence of other infections (ear, nose, throat[5]; urinary tract, etc.), pinworm infestations,[6] and masturbation. Most prefer broad-spectrum antibiotics or sulfonamides as specific therapy. Schauffler now restricts the use of estrogens to the so-called senile vaginitis of children and claims excellent results.[4] Teton and Treadwell[7] in their report in 1956 treated most of their cases with broad-spectrum antibiotics or sulfonamides. Two cases were treated with oral estrogens alone with good results.

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Data

This report covers 35 cases of vaginitis in children who were treated in the Pediatric Out-Patient Department of The New York Hospital between the years 1952 and 1956. This is an unselected series and represents almost our total experience during this period. An insignificant number of cases were discarded because of inadequate follow-up. It was decided arbitrarily that three months' time constituted a minimum follow-up, the average being slightly over two years.

The patients ranged in age from 18 months to 11 years, the greatest number being in the 4- to 7-year group.

The presenting complaint in all was a vaginal discharge. Ten cases were considered acute, i. e., under one month's duration, and 25 were considered chronic. In the latter group, we often obtained a history of three or four years' duration.

Method

A careful pediatric history was obtained in all patients, and the presence of ear, nose, or throat, as well as urinary tract, infections was noted. Ear, nose, or throat infections were present in three of the four chronic cases in which results were considered poor; these infections seemed to precede recurrences of the vaginitis in those patients.

Special attention was paid to the presence of emotional problems, masturbation, and allergic disorders (Table 1). The only poor results in the acute group were in two children, one of whom had severe asthma and the other, a severe emotional disorder. The latter was receiving psychiatric care at the time of her vaginitis.

TABLE 1.—*Related Conditions*

	No.
Total cases	35
Severe emotional problems	1
Masturbation	6
Severe asthma	2
Obesity	1
Parasitic infestation	2
Foreign body	1

All of the patients were examined by a gynecologist. Careful examination of the vulva and vagina was performed, and the degree of vaginitis was graded as mild or moderate-to-severe. An x-ray film of the abdomen was obtained in some patients.

Laboratory Findings

In 34 of the cases a bacterial culture of the vaginal exudate was obtained. All showed a mixed flora, the most common organisms being hemolytic and nonhemolytic Staphylococcus and Streptococcus, Proteus vulgaris, Escherichia coli, Aerobacter aerogenes, pneumococci, and others. No Gram-negative intracellular diplococci were reported.

The stool was inspected for ova and parasites in many cases. Two were positive, one for Enterobius vermicularis and the other for Trichuris trichiura. Both were treated with an appropriate antihelminthic agent. In the case of the trichuriasis the vaginitis healed promptly, but in the case of the vermicularis there were many recurrences (only one course of treatment was given).

Therapy

The duration of the disease and the history of previous treatment was used as a guide to the type of therapy instituted. In general, the mild acute cases were treated with antibiotics alone (oxytetracycline and chlortetracycline, 25 mg. per kilogram per day for one week). Those that had primarily a vulvitis with minimal vaginitis were treated with local measures. The more severe cases, especially those of a chronic nature, were usually treated with antibiotics in combination with estrogens (estrogen vaginal suppositories of 1,000 I. U. and Dienestrol cream, 3 ml. per day for 30 days). In the latter group, antibiotics were usually omitted if they had been used in previous treatment.

Results

Seven of the ten acute cases were healed regardless of the severity of the vaginitis (Table 2). There were recurrences in three cases, two of which were complicated by emotional problems and recurrent ear, nose, and throat infections.

Of the 25 chronic cases, 14 had received previous treatment consisting primarily of local measures, although some were given antibiotics. The type of previous treatment did not affect the results we obtained. Satisfactory cures were registered in 19 patients and poor results were evident in six (Table 3). Of these six, one had Enterobius vermicularis in the stool and one had severe asthma. In the remaining four patients, there was no relationship between the failure

TABLE 2.—*Cases of Acute Vaginitis*

Cases		Type of Therapy		Good Results, No.
A. Mild	5	Antibiotics	2	2
		Estrogens	1	1
		Local measures	2 *	1
B. Moderate to severe	5	Antibiotics + estrogen	5	3

* One of related conditions present (Table 1). Good results in 7 out of 10 cases.

TABLE 3.—*Cases of Chronic Vaginitis*

Cases		Type of Therapy		Good Results, No.
A. Mild	13			
1. Previous treatment	8	Antibiotics + estrogen	2	1
		Estrogens	4	3
		Local measures	1	1
		Estrogens + antihelminthic	1 *	0
2. No previous treatment	5	Antibiotics + estrogen	1	1
		Local measures	1	1
		Antibiotics	2	2
		Antihelminthic	1	1
B. Moderate to severe	12			
1. Previous treatment	6	Antibiotics + estrogen	4	2
		Estrogens	1	1
		Antibiotics	1	1
2. No previous treatment	6	Antibiotics + estrogen	3 †	2
		Antibiotics	2	2
		Removal of foreign body	1	1

* Cases with Enterobius vermicularis in the stool.

† One of related conditions (Table 1) present in one case. Good results in 5 out of 8 mild cases with previous treatment, in 5 out of 5 mild cases with no previous treatment, in 4 out of 6 moderate-to-severe cases with previous treatment, and in 5 out of 6 moderate-to-severe cases with no previous treatment.

and the type or duration of therapy that had been used previously.

Conclusions

From these results we feel that the duration of the vaginitis and the presence of related conditions are of greater prognostic importance than the type of therapy used or a history of previous treatment. Therefore, vaginitis in children should be treated promptly, and a careful search for any foci of infection must be made.

Treatment should consist of only local measures in the mild cases, with the addition of antibiotics in the more severely affected patients. We recommend that antibiotics be given in therapeutic dosage as previously outlined, for at least one week's duration. The local use of estrogens can be restricted to those cases which do not respond to the above regimen.

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REFERENCES

1. Lewis, R. M.: Studies of Effect of Theelin on Gonorrheal Vaginitis in Children, Am. J. Obst. & Gynec. 26:593-599 (Oct.) 1933.

2. TeLinde, R. W., and Brawner, J. N., Jr.: Experiences with Amniotin in Treatment of Gonococcal Vaginitis in Children, Am. J. Obst. & Gynec. 30:512-523 (Oct.) 1935.

3. Benson, R. A., and Weinstock, I.: Gonorrheal Vaginitis in Children: A Review of the Literature, Am. J. Dis. Child. 59:1083-1096 (May) 1940.

4. Schauffler, G. C.: Pediatric Gynecology with Sections on Urology and Proctology, Ed. 3, Chicago, The Year Book Publishers, Inc., 1953, p. 318.

5. Boisvert, P. L., and Walcher, D. N.: Hemolytic Streptococcal Vaginitis in Children, Pediatrics 2:24-29 (July) 1948.

6. Bumbalo, T. S.; Gustina, F. J., and Oleksiak, R. E.: Treatment of Pinworm Infection (Enterobiasis); Comparative Study of 3 Oxyuricides, J. Pediat. 44:386-391 (April) 1954.

7. Teton, J. B., and Treadwell, N. C.: The Management of Nonspecific Vulvitis in Children, Am. J. Obst. 72:674-676 (Sept.) 1956.

Clinical Notes

Successful Treatment of Cardiac Arrest During Exchange Transfusion

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Introduction

Much consideration has been given to the potentially serious disturbances of electrolyte balance, blood volume, and other factors of homeostasis which can occur during exchange transfusion. The cardiotoxic effects of potassium coupled with hypocalcemia are well recognized. And yet the occurrence of cardiac arrest, which would be the expected clinical outcome of these derangements, has been reported with surprising rarity.

Pew[1] reported a case of cardiac arrest occurring during exchange transfusion, which was managed successfully by thoracotomy and cardiac massage. We wish to draw attention to another example of this phenomenon in order that it may be more frequently recognized and favorably treated.

Report of a Case

This white boy appeared to be in excellent condition at birth, though he weighed only 4 lb. 1 oz. There was a Grade 2 systolic murmur on the left of the sternum. Thirty-six hours after birth, jaundice appeared, although liver and spleen were not palpable. Laboratory studies revealed the following findings: bilirubin 10 mg.; hemoglobin 16.8 gm.; Coombs' test negative. The blood smear showed occasional erythroblasts but no spherocytes. The baby's blood type was B, Rh-negative, and the mother's A, Rh-positive. Twelve hours later the bilirubin had risen to 15.1 mg. and the hemoglobin was down to 13.0 gm.

It was felt that the baby probably had an ABO type of erythroblastosis, and he was prepared for an exchange transfusion. He now weighed only 3 lb. 10 oz. The donor blood, Type O, Rh-negative, had been freshly drawn two hours before the transfusion. It was neither refrigerated nor subsequently warmed.

The exchange was performed through a right femoral cut-down with use of a 16 gauge polyethylene catheter inserted for a distance of about 2 in. The transfusion was carried out by use of a 10 cc. syringe, and 1 cc. of 10% calcium gluconate was slowly injected after 100 cc. of replacement.

The infant tolerated the procedure well until 150 cc. of blood had been exchanged, when the anesthetist exclaimed that the heart had suddenly stopped beating. The pulse rate immediately before asystole had been 132 per minute with a regular rhythm.

Artificial respiration with 100% oxygen was begun immediately. While one of us prepared to incise the chest, the other injected 0.2 cc. of epinephrine (1:2,600) intravenously. When this produced no response, the left chest was incised vertically through the second to the sixth costal cartilages and cardiac manipulation was begun. (The vertical rather than the classical fifth interspace or "hockey stick" thoracotomy incision was necessitated by the limiting nature of the restraints and the board to which the baby was strapped.)

Massage was performed by compressing the heart against the sternum at a rate of 120 per minute. Spontaneous cardiac action was resumed after less than one minute of massage, and in less than two minutes the contractions had become vigorous enough that manual compressive assistance was no longer necessary.

A surgeon was called to close the chest, and artificial positive pressure respiration was continued until spontaneous breathing was resumed some 15 minutes after the closure was completed.

Immediately after the resuscitation procedure the exchange transfusion was continued without any further complications until 400 cc. of blood had been exchanged. The postoperative billirubin level was 5.8 mg.

Postoperatively the baby did very well, and at the time of this writing he is 18 months old and

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in all respects a normal baby, with developmental appraisal revealing no hint of retardation or brain damage.

Comment

Taylor, Grisdale, and Stewart[2] have recently reviewed the subject of cardiac arrhythmia and arrest during exchange transfusion. They have summarized 10 cases, including 2 of their own, which shared in common the electrocardiographic features of sudden onset of arrhythmia, 2:1 heart block, or the clinical features of sudden cardiac arrest. In the majority of these patients it was difficult to ascertain the exact pathology leading to this phenomenon. They suggested that one or a combination of factors, such as hyperpotassemia, hypocalcemia, acidosis, prematurity, the disease process itself, or other unknown and unsuspected conditions, may lead to the disruption of cardiac function.

Cardiac arrest should be considered as a possibility during every exchange transfusion. We feel that any patient with clinical or electrocardiographic signs of asystole should have the benefit of cardiac massage if conservative therapy has failed to stimulate immediate return of normal cardiac rhythm. Therefore, it is desirable that exchange transfusion be performed in the operating room, with a trained observer constantly monitoring the infant's vital signs in order that proper therapy may be initiated the moment any untoward reaction occurs.

Summary

A case of cardiac arrest occurring in a premature baby during exchange transfusion is reported. The patient was treated with thoracotomy and cardiac massage with successful outcome. Some precautionary measures are advocated which we believe played a large part in saving the baby.

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REFERENCES

1. Pew, W. L.: Cardiac Arrest During Exchange Transfusion, J. Pediat. 47:645, 1955.

2. Taylor, W. C.; Grisdale, L. C., and Stewart, A. G.: Unexplained Death from Exchange Transfusion, J. Pediat. 52:694, 1958.

Multiple Metaphyseal Fibrous Defects

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A relatively common bone finding in the younger age group, nonosteogenic fibroma usually occurs as a solitary metaphyseal lesion eccentrically placed and abutting on the cortex of a long bone of a lower extremity. Presentation of the following case seems warranted by the multiplicity of defects as well as by the presence of one lesion in the upper extremity. These lesions are usually incidental findings and are considered benign developmental defects rather than true neoplasms. We prefer the term metaphyseal fibrous defect as used by Hatcher[1] and accepted by Cunningham and Ackerman.[2]

Report of a Case

A 13-year-old boy was admitted to the hospital for treatment of fractures of the right patella and carpal navicular. Roentgenograms at this time showed a bone lesion involving the right lower femoral shaft. The incidentally discovered lesion was asymptomatic and unrelated to the trauma. Radiographic bone survey demonstrated multiple (six) cyst-like defects confined to the metaphyseal portions of several long bones, including right and left lower femoral shafts, proximal left tibia (through which a recent "pathological" fracture had occurred), proximal right tibia, left fibula, and right radius. The radiographic appearance of the lesions was interpreted as being "individually consistent with nonosteogenic fibromata." A biopsy of the left upper tibia was reported as consistent with giant-cell tumor of bone. However, because of the radiographic findings, age of the patient, and multiplicity of lesions, this diagnosis was disputed. Additional studies were done to rule out polyostotic fibrous dysplasia, hyperparathyroidism, and other bone dyscrasias. Because of persistence of the lesions, a second biopsy of the left upper tibia was done two years later. At this time there was a definite change in the microscopic appearance with the presence of multinucleated giant cells, proliferating fibroblasts, hemosiderin-laden macrophages, cholesterol clefts, and occasional foam cells. This picture was interpreted by the pathologist and consultants as secondary change related to repair. There was no evidence of neoplasm.

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Fig. 1 (Sept. 1, 1954).—Left knee, showing multiloculated appearance of lesion in upper tibia, as well as a very small lesion in the corresponding portion of the fibula.

Fig. 2 (Sept. 1, 1954).—Right lower femur, showing lesion elevating and thinning cortex.

Fig. 3 (Sept. 1, 1954).—Left lower femur, showing similar lesion symmetrically located in opposite leg.

Fig. 4. (May 24, 1957).—Left lower femur. This later examination is of interest in showing migration and reduction in size of lesion seen in Figure 3. Note new foci distal to this lesion, suggesting intermittent production of fibrous defects.

Follow-up roentgenograms four years after the original examination revealed some regression of the lesions, which had tended to migrate away from the epiphyses with bone growth. The lesions have remained asymptomatic, and the patient has since entered military service.

Summary

This case is of interest primarily because of the multiplicity of metaphyseal fibrous defects. In addition it emphasizes the necessity of careful correlation of the clinical, radiological, and pathological findings in arriving at a definitive diagnosis of bone lesions.

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REFERENCES

1. Hatcher, C. H.: Pathogenesis of Localized Fibrous Lesions in the Metaphyses of Long Bones, Ann. Surg. 122:1016-1030 (Dec.) 1945.

2. Cunningham, J. B., and Ackerman, L. V.: Metaphyseal Fibrous Defects, J. Bone & Joint Surg. 38-A:797-808 (July) 1956.

Abstracts from Current Literature

American Heart Journal, St. Louis
Abstracted by F. Kathyrn Edwards, M.D.

55, No. 5 (May) 1958

* The Mean Manifest Electrical Axis of the Ventricular Activation Process (AQRS) in Congenital Heart Disease: A New Approach in Electrocardiographic Diagnosis. Demetrio Sodi-Pallares, Fulvio Pilaggi, Fernando Cisneros, Paulo Ginefra, Bilivar Portillo, Gustavo A. Medrano, and Abdo Bisteni.—p. 681.

The Clinical Significance of Cardiac Gallop Rhythm. Archibald W. Sloan.—p. 715.

Congenital Stenosis of Pulmonary and Aortic Valves with Patent Ductus Arteriosus. Arthur J. Thomas.—p. 724.

An Evaluation of the Serum Glutamic Oxalacetic Transaminase Activity in Pericarditis. Robert B. Kalmansohn and Richard W. Kalmansohn.—p. 739.

Retrograde Aortography under Hypothermia in Infancy and Early Childhood. Howard A. Joos and John L. Johnson.—p. 743.

Pericarditis and Myocarditis Caused by Toxoplasma: Report of a Case and Review of the Literature. Juha Hakkila, Heikki M. Frick, and Pentti I. Halonen.—p. 758.

Isolated Congenital Absence of the Right Pulmonary Artery: A Caution as to Its Diagnosis and a Proposal for Its Embryogenesis: Report of a Case with Review. Lawrence J. Schneiderman.—p. 772.

The Hemodynamic Results of Open Heart Surgery: Preliminary Report. Henry A. Zimmerman and Earle B. Kay.—p. 791.

Primary Hypertension and Hypertensive Disease in Early Childhood. Nemat O. Borhani and Richard E. Lee.—p. 796.

55, No. 6 (June) 1958

Estimation of Cardiac Output in Man by Dye Dilution Method Using an Automatic Computing Oximeter. P. Sekelj, D. V. Bates, A. L. Johnson, and W. Jegier.—p. 810.

Pitfalls in the Diagnosis of Pulmonary Hypertension. Jonas Brachfeld, Attilio Reale, and Harry Goldberg.—p. 905.

* Direct Left Ventricular Puncture in the Evaluation of Aortic and Mitral Stenosis. Paul N. Yu, Frank W. Lovejoy Jr., Bernard F. Schreiner, Robert H. Leahy, C. Alpheus Stanfield, and Heinz Walther.—p. 926.

56, No. 2 (Aug.) 1958

Congenital Mitral Atresia. Walter M. Teller.—p. 304.

* Aneurysm of the Ascending Aorta Caused by Congenital Syphilis. Hallard W. Beard and Robert G. Thompson.—p. 313.

56, No. 3 (Sept.) 1958

Cardiac Dextroposition: Hypoplasia of the Right Pulmonary Artery with Right Venous Pulmonary Drainage into the Inferior Vena Cava. M. Torner-Soler, I. Balaguer-Vintro, and J. Carrasco-Azemar.—p. 425.

Coronary Arteriovenous Aneurysm: Review of the Literature. Jeppe Schultz.—p. 431.

* The Use of Digoxin in Infants and Children. Anna J. Hauck, Patrick A. Ongley, and Alexander S. Nadas.—p. 443.

56, No. 5 (Nov.) 1958

Serum Electrolyte Observations Following Extracorporeal Circulation. Daniel M. Baer, John J. Osborn, Herbert A. Perkins, Denis G. Melrose, Alan Norman, and Frank Gerbode.—p. 652.

The Origin and Interpretation of Murmurs in Coarctation of the Aorta. Merrill P. Spencer, Frank R. Johnston, and Jesse H. Meredith.—p. 722.

Situs Inversus Totalis Associated with Complex Cardiovascular Anomalies. Karl J. Schmutzer and Leonard M. Linde.—p. 742.

* Pathologic Study of Persistent Common Atrioventricular Canal. Coolidge S. Wakai and Jesse E. Edwards.—p. 779.

The Mean Manifest Electrical Axis of the Ventricular Activation Process (AQRS) in Congenital Heart Disease: A New Approach in Electrocardiographic Diagnosis.—The mean manifest electrical axis (AQRS) as determined by Bayley's triaxial system was correlated with the type of congenital heart disease in an analysis of 1,331 electrocardiograms.

The analysis revealed the following in cyanotic congenital heart disease:

A. Axis in Bayley's Sextant VI (0+59 Degrees).—The main malformations were Ebstein's disease, tricuspid atresia, and single ventricle.

B. Axis in Bayley's Sextant I (−1 to −60 Degrees).—The malformation with the highest incident in this axis is tricuspid atresia. Less frequently seen in this sextant are presistent common atrioventricular canal, tricuspid atresia, Ebstein's disease, and single ventricle.

C. *Axis in Bayley's Sextant II (−61 to −120 Degrees).*—The most common malformation in this sextant is persistent common atrioventricular canal and tetralogy and trilogy of Fallot.

D. *Axis in Bayley's Sextant III (−121 to ±180 Degrees).*—The congenital lesion with the highest incident is tetralogy of Fallot.

E. *Axis in Bayley's Sextant V (Between +119 and +60 Degrees).*—Every cyanotic entity in this series was found in this sextant.

The analysis revealed in acyanotic congenital heart disease:

A. *Axis located in Bayley's Sextant VI (between 0 and +59 degrees).* The anomaly seen most frequently in this sextant was patent ductus without pulmonary hypertension. Coarctation of the aorta was the next most common lesion.

B. *Axis located in Bayley's Sextant I (−1 to −60 degrees).* The most frequent acyanotic anomaly in this sextant is coarctation of the aorta.

C. *Axis located in Bayley's Sextant II (−61 to −120 degrees).* The most frequent defect in this sextant is ventricular septal defect, with Eisenmenger's complex being second most common.

The authors state that the combination of the determination of the AQRS in the frontal plane with the knowledge of the electrocardiographic pattern of each congenital heart malformation permits the diagnosis of the anomaly in a large number of cases.

Direct Left Ventricular Puncture in the Evaluation of Aortic and Mitral Stenosis.—Data obtained from direct left ventricular puncture via an anterior percutaneous approach is presented. The surgical approach used was that previously described by Brock and associates.

Thirty patients (ten with aortic stenosis, five with both mitral and aortic stenosis, eight with mitral stenosis and seven with other cardiovascular diseases) were studied. The authors caution against using this approach in myocardial infarction or severe myocardial disease. There were no major complications in the 30 cases presented.

In patients where calculated aortic size was less than 0.5 cm^2 aortic flow was reduced and there was elevation of the end diastolic pressure in the left ventricle.

Aneurysm of the Ascending Aorta Caused by Congenital Syphilis.—A case of aneurysm of the ascending aorta occurring in a 20-year-old man is reported. Although no autopsy confirmation is available, the history suggests congenital syphilis as the etiology.

The effects of congenital syphilis on the cardiovascular system are reviewed. These consist the following:

1. Myocardial involvement, which occurs in infants as a diffuse interstitial myocarditis or focal nodular myocarditis and which may cause sudden death in infancy.
2. Aortitis of infancy, which is histologically identical to early aortitis of acquired syphilis and which may result in aortic aneurysm in older children and young adults.
3. Aortitis and aneurysm in older children and young adults which is pathologically like that of acquired syphilis.
4. Peripheral vascular lesions, which consist of endarteritis and may be widely distributed throughout the body.

The incidence of aortic aneurysm resulting from aortitis in infants with congenital syphilis is apparently very low. The authors state that Hinrichsen found only 25 cases from a review of the literature up to 1943.

The Use of Digoxin in Infants and Children.—This article reports the results of the treatment of 86 children with digoxin.

Digoxin is a purified glycoside of digitalis lanata which can be given orally, intramuscularly or intravenously. The parenteral solution of digoxin in 40% propylene glycol and 10% ethyl alcohol has its peak of action in two hours when given intravenously and in eight hours when given intramuscularly.

The fairly rapid rate of elimination of digoxin is its greatest advantage over digitoxin and digitalis leaf. Toxic symptoms disappear within a few hours to 48 hours.

The dosage schedules used in this study was 0.03±0.01 mg. per pound body weight, generally administered either as 0.01 mg. of digoxin per pound at 6- to 8-hour intervals until an adequate response was obtained or toxicity noted, or given as 0.02 mg. of digitoxin per pound and then 0.01 mg. per pound at six- to eight-hour intervals until effects or toxicity was noted. The parenteral dosage was calculated at two-thirds of the oral dosage.

The daily maintenance dosage was estimated to be one-fourth to one-third of the initial digitalizing dose and was given in two equally divided doses at twelve hour intervals.

The authors found clinical signs of toxicity difficult to evaluate since anorexia, nausea, and vomiting are frequent findings in any group of sick hospitalized infants and children. The electrocardiogram proved to be the most reliable, and frequently the only, sign of toxicity. Thirty-six patients had electrocardiographic evidence of toxicity. Disturbances in atrioventricular conduction (28 children developed first-degree heart block; 10 children developed ectopic beats; 3 developed nodal rhythm) were the usual signs of toxicity by electrocardiogram. Children with myocardial disease were unusually sensitive to digoxin toxicity.

The authors stress that the dosage schedule must be regulated for each individual although average doses ranged as follows:

	Digitalization	*Daily Maintenance*
Children up to 2 years of age	0.04 mg/lb.	0.013 mg/lb.
Children over 2 years of age	0.02 to 0.03 mg/lb.	0.007 to 0.01 mg/lb.

Pathologic Study of Persistent Common Atrioventricular Canal.—This is a report of the examination of 28 hearts with persistent common atrioventricular canal. The malformations are divided into the complete type, the intermediate type, and the partial type.

In the comp'ete form of persistent common atrioventricular canal, there is anatomic evidence of lack of fusion of the two atrioventricular endocardial cushions with each other and with atrial and ventricular septal complexes. This is manifest by a cleft through both the anterior leaflet of the mitral valve and the septal leaflet of the tricuspid valve as well as an intraventricular communication through a subvalvular space above the ventricular septum and an atrial defect which is low and has an arch-shaped upper border.

The partial form has developed further toward a normal heart. There is a cleft in the anterior leaflet of the mitral valve as anatomic evidence that the dorsal and ventral atrioventricular cushions failed to fuse on the left. On the right side the endocardial cushions are fused and the tricuspid valve leaflets are normal or nearly normal. The atrial defect is much like that in the complete form, but there is usually no defect in the ventricular septum.

In the intermediate form there is anatomic evidence that minute extensions of the dorsal and ventral atrioventricular cushions fused at their mid line, but not sufficiently to eliminate the cleft in the mitral or tricuspid leaflets. The clefts in the valve leaflets are present on both valves, but a narrow bridge of valvular tissue joins the anterior half of each of the two cleft atrioventricular valvular leaflets with their respective posterior halves just above the ventricular septum. The atrial septal defect is much like that in the complete form. The membranous septum is defective below the atrioventricular valves.

Of the 28 cases whose hearts were examined, 6 had associated Mongolism and 5 of these had cyanosis. The associated defects of the cardiovascular system seen in the 28 cases consisted of patent foramen ovale, patent ductus arteriosis, double mitral valve, and a variety of less common lesions.

There was no difference in the incidence of persistent common atrioventricular canal between the two sexes. Death at an early age was common. Of 25 cases alive at birth, only 4 lived past 6 years of age. The most common cause of death was congestive heart failure. Only one death was due to subacute bacterial endocarditis.

American Journal of Mental Deficiency, Albany, N. Y.

Abstracted by Kurt Glaser, M.D.

62, No. 1 (July) 1957

Mental Retardation: A Review of Mental Health Implications—A Reprint. Leonard J. Duhl.—p. 5.

A Group Therapy Experiment with Mothers of Mentally Deficient Children. Joseph E. Rankin.—p. 49.

Tuberculosis Control in Schools for Mental Defectives. George E. Spencer.—p. 56.

The Effect of Reserpine in 200 Mentally Retarded Children. William H. Timberlake, Elizabeth H. Belmont and John Ogonik.—p. 61.

* Pigmentary Retinal Lipoid Neuronal Heredodegeneration (Spielmeyer-Vogt Disease). Julius Hoffman and John P. Riepenhoff.—p. 67.

62, No. 2 (Sept.) 1957

* Speech and the Mentally Retarded Child. Stanley Goertzen.—p. 244.

Effects of Serpasil and Accent on Behavior, Intelligence, and Physiology. Philip D. Pallister and Robt. R. Stevens.—p. 267.

Clinical Experience with Serpasil and Thorazine in Treatment of Disturbed Behavior of Mentally Retarded. Isaac N. Wolfson.—p. 276.

Effects of Methyl-Phenidylacetate (Retalin) on Drug-Induced Drowsiness in Mentally Retarded Patients. Jas. M. Levy, B. E. Jones and Hugh T. Croley.—p. 284.

The Clinical Use of Reserpine and Chlorpromazine in the Care of the Mentally Deficient. Alfred H. Johnson and Chas. H. Martin.—p. 292.
(The last three articles describe observations of the beneficial effect of Reserpine and Chlorpromazine on the behavior of institutionalized mentally retarded children.)

62, No. 3 (Nov.) 1957

Family History of a Mongolian Girl Who Bore a Mongolian Child. A. T. Rehn.—p. 496.
A Woman with Mongolism and Her Child. Hans Forssman and Torsten Thysell.—p. 500.
* Mandibulofacial Dysostosis with Oligophrenia in Siblings. Robert Gibson.—p. 504.
* Accelerated Intellectual Growth and Personality Development as Seen in Phenylketonuric Subjects During Medical Treatment. Dorothy Clader.—p. 538.

Pigmentary Retinal Lipoid Neuronal Heredodegeneration (Spielmeyer-Vogt Disease).—The symptomatology of infantile amaurotic family idiocy (Tay-Sachs disease), late infantile amaurotic family idiocy (Jansky-Bielschowsky), juvenile amaurotic family idiocy (Spielmeyer-Vogt or Batten-Mayou), adult amaurotic family idiocy (Kufs), and congenital amaurotic family idiocy (Norman) is described. The authors do not share the belief of some that Spielmeyer's disease is the delayed form of infantile amaurotic family idiocy and also contend that historically the names of Batten-Mayou should be attached to this entity rather than Spielmeyer-Vogt. They suggest the descriptive name of pigmentary retinal lipoid neuronal heredodegeneration.

The case presentation of two sisters showed the onset to be between 5 and 8 years and the findings to consist of progressive impairment of vision with retinal pigmentation but no cherry-red spot. Optic atrophy occurs late; mental deterioration is progressive; paralysis occurs, and convulsions are severe. Speech is disturbed, the attention span shortened, and apathy and irritability occur. The family history was positive on the father's side.

The disease is inherited as a true recessive characteristic. The biochemical qualities of the lipoids are different from those in Tay-Sachs disease. The microscopic neuropathological findings resemble those of other forms of cerebromacular degeneration, but the ophthalmological signs differ inasmuch as the outer layers of the retina are affected.

Comment: While the authors of the article are concerned mainly with the nosology of this and related entities, the article presents a good, though brief, review of the symptomatology of these conditions, and its 80 references are an excellent source for further reading.

Speech and the Mentally Retarded Child.—This review of the literature (38 references) attempts to answer some important questions for those diagnosing and evaluating mentally retarded children.

Retarded speech development of the defective child deprives him of the stimulating and corrective experience of talking to others or being talked to; errors are therefore perpetuated and promotion of oral expression by social satisfaction is wanting.

In studies of large numbers of patients about one-third were found to have normal speech. The incidence and severity of speech defects increased with increasing degree of defectiveness.

The author points toward the need for differentiation between delayed speech, speech defects, and linguistic inadequacy. The commonest cause of delayed speech is mental subnormality, but illness or physical disability, lack of stimulation, oversolicitous parents, overly strict parents, intense shock, fright, or shame are also causes to be considered. The recognition of these causes of speech delay is important to avoid errors in classification of mentally normal children.

The author also describes the type and incidence of speech defects in various conditions as reported by different authors. The main goal of speech therapy for the mentally retarded is to facilitate adequate social development and adjustment.

Mandibulofacial Dysostosis with Oligophrenia in Siblings.—The cases of two brothers, both mentally retarded (I. Q. 46 and 48 respectively) and with the above condition, are described. In one child the physical symptoms were less typical than in the other. The father's "exceptionally long face, large and slightly irregular ears and mild but definitely anti-Mongoloid slant of the eyes" were considered signs of an incomplete form of the same condition. The parents were unrelated and there was no family history of abnormalities. The first child of this marriage, a girl, was normal

Accelerated Intellectual Growth and Personality Development as Seen in Phenylketonuric Subjects During Medical Treatment.—Progressive psychological evaluation and behavioral studies of three phenylketonuric children were made over a period of about one year. The I. Q. of the two 4-year-old children increased from 35 and 37 respectively to 61 and 56, respectively, over the observation period during which a special diet was given. The I. Q. of the third child was 100 when first seen at two months of age and remained the same. The behavioral improvement of the two older children was dramatic.

The author warns of premature generalizations from these three observations over a period of only about one year.

American Journal of Orthopsychiatry, Menasha, Wis.
Abstracted by Kurt Glaser, M.D.

27, No. 1 (Jan.) 1957

* The Evaluation of Rehabilitation in the Individual Panel, 1955. Morton A. Seidenfeld, Chairman; Melvin A. Glasser, Lawrence Edwin Abt, Saul H. Fisher, Pauline Moore Ryman and Mary E. Switzer.—p. 9.
* Psychiatric Aspects of Familial Dysautonomia. Alfred M. Freedman, William Helme, Joan Havel, Marjorie J. Eustis, Conrad Riley and William S. Langford. Discussant: Reginald S. Lourie.—p. 96.

27, No. 3 (July) 1957

A Study of the Problem of Mental Retardation in a Large Community. Robert G. Ferguson.—p. 490.
Present-Day Society and the Adolescent. George E. Gardner.—p. 508.
Motivation and Frustration in Delinquency. Richard L. Jenkins.—p. 528.
* The Role of a Psychiatrist in a Well-Baby Clinic. Ilse Judas, Eugene I. Falstein, and Robert S. Mendelsohn.—p. 621.

28, No. 1 (Jan.) 1958

The Emotional Significance of Acquired Physical Disfigurement in Children. E. Jane Watson and Adelaide M. Johnson.—p. 85.
Delinquency—A Laboratory for Public Health Psychiatry. Harris B. Peck.—p. 134.
* Emotional Reactions to Medical Procedures and Illness in a Hospital Child Psychiatry Unit. Helen A. Sutton, Eugene I. Falstein and Ilse Judas.—p. 180.

The Evaluation of Rehabilitation in the Individual. Panel, 1955.—In this panel discussion many aspects of rehabilitation are considered which the physician often does not study or does not consider within his realm of influence, without which, however, the entire rehabilitation program may become ineffective for the individual patient. Although this article does not deal specifically with the rehabilitation of children, most factors are applicable, with modifications, to all ages.

In "Community and Group Factors" M. A. Glasser points out how community and cultural factors influence the patient's orientation toward rehabilitation and what role the "health worker" plays in helping the patient to adjust to his handicap and to cooperate in a rehabilitation program. For an "Assessment of Rehabilitation Potential" (L. E. Abt) the Menninger Health-Sickness Rating Scale is suggested. It contains the following points: (1) need for protection and support vs. ability to function autonomously; (2) seriousness of symptoms; (3) discomfort and distress; (4) effect on environment; (5) degree to which patient can utilize his abilities; (6) quality of interpersonal relationship, and (7) patient's interests. For assessing rehabilitation progress a similar scale may be used.

The role of the psychiatric team as described by S. H. Fisher starts in the evaluation clinic before rehabilitation work begins, in the form of help in the formulation of the program and evaluation of the degree to which the patient can make use of the program. The evaluation includes intellect, organic brain deficit, personality features, evidence of neurosis, psychosis or sociopathy, motivation, patient's concept of his disability and the rehabilitation service, and possible anticipation of psychological problems of management. The psychiatric team deals with some problems on a consultative level, with others more intensively in weekly conferences of the entire staff. Some case histories illustrate the practical aspect of the team's functioning.

P. M. Ryman describes the contributions by the medical social worker and M. E. Switzer the aspects of vocational rehabilitation.

Psychiatric Aspects of Familial Dysautonomia.—Six girls and eight boys, ranging in age from 3.8 to 13.4 years, with the above disease were studied by a psychiatric team. The study consisted of psychiatric interviews with child and parents, a study of all events during one week at home, tabulation of hospital data and psychological testing of the child. A parent

group conducted over a period of three years provided information on the problems confronting the parents of these children.

The psychological findings included excessive demands and dependency of the children with successful manipulation of the parents, avoiding direct and intimate contact between parents and child. Relationship with siblings was usually better, with peers one of submissive behavior to make friends. Other female members of the family were found to have a better relationship with the child than the mother, although they were always kept at a distance. The children were restless, impulsive, and with inadequate coordination. Intellectual functioning, although generally believed to be retarded, was found adequate in some subtests reflecting abstract thinking. In general these children resemble those suffering from diffuse organic brain disorder.

All cases showed emotional disturbance, which the authors explain as a reaction of the parents to the disturbed homeostasis of the child which in turn originates from his central nervous system derangement. The fear, resentment, and guilt of parents lead to their permissiveness and vacillation, thus providing an unstable environment for the child who reacts with anxiety and insecurity and thus further increases his homeostatic disturbances.

Therapeutically the authors have tried to stabilize the home set-up by parents group discussions and by setting up a rigid routine for the child's activities. Chlorpromazine and individual psychotherapy has been found useful for the child himself.

The Role of a Psychiatrist in a Well-Baby Clinic.—At the Well-Baby Clinic of Michael Reese Hospital pediatric residents follow mother and child through their two years of residency. A psychiatrist attends the sessions and holds group discussions with the residents and other staff members of the Clinic.

The pediatric resident is encouraged to elicit signs and symptoms in the emotional sphere, especially around areas of psychosexual development, jealousy, reaction to separation, and signs of infantile neuroses such as night fears, bed wetting and thumb sucking. Mother-child relationship and family relationships were elicited by observation of the mother's reaction to the child's behavior, and by specific questioning. The pediatrician was encouraged to observe the verbal and nonverbal communications of the mother as they applied to the doctor-patient relationship.

The psychiatrist was alert to take cues from the pediatrician when to begin to talk with the mother, leaving decisions with regard to disposition and further study to the pediatrician. The pediatrician's reaction to the psychiatrist varied according to his own personality, and the psychiatrist was guided in the intensity of her work by the pediatrician's acceptance. Most pediatricans felt that their relationship with the patient improved and that their experience in working with mother and child became more meaningful and enjoyable. They learned how to cope with most problems and to judge when and how to refer for psychiatric care. The psychiatrist found in the experience the opportunity of observing emotional development in its normal and pathological forms from the early beginnings of life rather than retrospectively.

Comment: This paper and others (ibid. 28:506; AM. J. DIS. CHILD. 94:143) should stimulate more extensive use of this part of training for pediatric residents.

Emotional Reactions to Medical Procedures and Illness in a Hospital Child Psychiatry Unit.—The authors studied over a two-year period "what procedures or illnesses were most frightening" to three girls and two boys, aged 6 to 10 years, admitted to the Michael Reese Hospital for psychiatric disturbances. The children were exposed to routine medical procedures and treatments as needed for intercurrent infections or injuries.

The most feared diagnostic procedures were nose and throat cultures and rectal swabs. The children were more concerned over medical procedures than over their illness. Their response was strongly conditioned by their own psychopathology. Procedures which the child could observe were less threatening. Injections caused aggravation of the child's psychiatric symptoms and produced a variety of defense reactions. Most traumatic was isolation for reasons of infection, which caused paranoid and compulsive reactions, withdrawal or a fight for contact with the outside; if arrangements were made for the child to see other children and to know that the doors were not locked, the reactions were milder. The children showed some common fantasies, such as blood-stained nurses and ghosts.

In group playing they at first portrayed nurses as sadistic adults, but later on as benign and protective figures. Subconsciously children and nurses considered some procedures as punitive, and psychiatric nurses found it difficult to administer them, especially if they were contrary to the prescribed psychiatric attitudes.

The recommendations pointed toward a reduction of medical procedures of any kind in a psychiatric unit dealing with emotionally disturbed children, and close communication among psychiatrist, pediatrician, and nurses concerning potential emotional trauma.

American Journal of Pathology, Ann Arbor, Mich.
Abstracted by Jay Bernstein, M.D.

34, No. 5 (Sept.-Oct.) 1958

Hypertensive Vascular Disease as a Consequence of Increased Arterial Pressure. G. M. C. Masson, L. J. McCormack, H. P. Dustan and A. C. Corcoran.—p. 817.

* Histologic and Histochemical Studies of the Rabbit Glomerulonephritis Produced by Specific Anti-Kidney Duck Serum. M. Wachstein and K. Lange.—p. 835.

The Juxtaglomerular Cells in Man and Their Relationship to the Level of Plasma Sodium and to the Zona Glomerulosa of the Adrenal Cortex. James A. Pitcock and Phyllis M. Hartroft.—p. 863.

Electron Microscopy of the Mammalian Renal Glomerulus; the Problems of Intercapillary Tissue and the Capillary Loop Basement Membrane. R. K. F. Pak Poy.—p. 885.

The Properdin System in Transplantable Cancer (Gardner Lymphosarcoma $6C_3HED$). Peter A. Herbut and William H. Kraemer.—p. 911.

Chemical Mediators in Relation to Cytological Constituents in Inflammation. Valy Menkin.—p. 921.

Cytopathology of Human Enteric Viruses in Tissue Culture. Dorothy N. Shaver, Almen L. Barron and David T. Karzon.—p. 943.

Inherited (Congenital) Cataract in the Dog. A. C. Andersen and Fred T. Shultz.—p. 965.

Identification of the Anatomic Defect in Pseudoxanthoma Elasticum. Edwin R. Fisher, Gerald P. Rodnan and Albert I. Lansing.—p. 977.

Histologic and Histochemical Studies of the Rabbit Glomerulonephritis Produced by Specific Anti-Kidney Duck Serum.—Nephrotoxic duck antiserum was used to induce in rabbits a reproducible form of glomerulonephritis, accompanied by proteinuria, azotemia, hypercholesterolemia, hypoalbuminemia, and diminution of serum complement. The course of the disease was divided into four phases characterized by histologic and histochemical alterations:

1. An initial incubation phase, lasting four days, during which the animals were outwardly normal. At the end of this period an increase in glomerular cellularity appeared.

2. A proliferative and exudative phase, lasting from the fifth to eighth days, during which generalized edema and proteinuria appeared. Thrombi and inflammatory and proliferative changes appeared in the glomeruli. Hyaline droplets appeared in the proximal convoluted tubules, and the mitochondria were diminished. After several days proliferation of the cells in Bowman's capsule took place, and some of the tubular droplets became disintegrated and discharged into the lumina. Alkaline phosphatase, 5-nucleotidase and glycerophosphatase activity were consistently reduced in the tubules during the latter half of this phase.

3. A proliferative phase, lasting from the 8th to 16th days, during which the blood urea nitrogen reached its highest levels. Capsular proliferation and basement membrane thickening were present in the glomeruli, and adenosine triphosphatase activity was increased. Tubular changes progressed to atrophy; hyaline droplets and all enzymatic staining, including esterase and dehydrogenase activity, were reduced.

4. A reparative phase, lasting till the 15th day, during which healing occurred. Glomeruli became fibrosed and hyalinized. Tubules were varying atrophic, normal and hypertrophic. Normal-appearing tubules gave normal enzymatic staining reactions, and only some DPN diaphorase activity could be demonstrated in atrophic tubules.

Histochemical alterations did not precede the appearance of histologic changes, and it is felt that the evidence somewhat supports the view that tubular alteration is secondary to the reabsorption of protein.

American Review of Tuberculosis and Pulmonary Diseases, New York
Abstracted by Edwin L. Kendig, Jr., M.D.

78, No. 4 (Oct.) 1958

The J. Burns Amberson Lecture: The Supporting Structure of Immunity in the Therapy of Tuberculosis. Esmond R. Long.—p. 499.

Antituberculous Activity of Thiocarbanidin in Vitro and in the Experimental Animal. W. Steenken, Jr., V. Montalbine, M. M. Smith, and E. Wolinsky.—p. 570.

* A Small Outbreak of Histoplasmosis. Thomas S. Hosty, Libero Ajello, Gordon D. Wallace, Julian Howell, and Jane Moore.—p. 576.

Studies of the PAS Salt of Isoniazid in the Treatment of Tuberculosis. L. C. Evander et al.—p. 637.

Antimicrobial Therapy of Tuberculosis. A Statement of the Committee on Therapy.—p. 656.

78, No. 5 (Nov.) 1958

* An Evaluation of Tuberculosis Case Finding by Tuberculin Testing and Some Observations of Histoplasmin Sensitivity Among Young School Children. Lawrence E. Wood, Michael L. Furcolow, and Myron J. Willis.—p. 667.

The Value of an Index of Maximal Expiratory Force in the Interpretation of Tests of Maximal Ventilatory Capacity. Maurice McGregor.—p. 692.

The Effect of Glucose on the Tuberculin Reaction in Tissue Culture. Frank A. Kapral and Warren R. Stinebring.—p. 712.

Bacteriologic and Clinical Significance of the Catalase Activity of Mycobacterium Tuberculosis. Otto Schweiger and Edit Vandra.—p. 735.

The Vital Staining Method for the Rapid Estimation of the Bacterial Count of BCG Vaccine. L. Greenberg et al.—p. 785.

A Semi-Synthetic Autoclavable Medium for a Routine Tuberculosis Laboratory. Lenore R. Peizer et al.—p. 788.

Lack of Circulating Antibodies After BCG Immunization as Assayed by the Globulin Titration Technique. Matthew H. Fusillo and Daniel L. Weiss.—p. 793.

The Pancreas in Experimental Tuberculosis. Guinea Pig Inoculation via the Intraperitoneal Route. Charles D. Brown.—p. 794.

Titration of Cord Formation as a Measure of Pathogenicity of Wild-Type Acid-Fast Bacilli, Typical and Atypical. H. M. Vandiviere et al.—p. 799.

Bacteriotropic Activity of Isoniazid in the Presence of Certain Other Compounds. Richard Urbancik.—p. 802.

Metabolism of Isoniazid by Mycobacterium Tuberculosis BCG with Reference to Current Theories of the Mode of Action. Jean Youatt.—p. 806.

A Small Outbreak of Histoplasmosis.—The authors report the result of an investigation of three cases of atypical pneumonia in one family, a 36-year-old father and two children, 3 and 5 years of age, respectively. The father's infection proved fatal.

Epidemiologic studies revealed that histoplasmosis was the cause of the respiratory infection, characterized by marked anorexia, low-grade fever, sore throat, cough, and depression, and pulmonary densities demonstrable on roentgenogram. Manure (probably from chickens), collected by the parent, was the probable source of infection.

While mycologic studies were not carried out on the children or on the parent during his illness, complement-fixation studies for influenza A and B, psittacosis, Q fever, and histoplasmosis were performed. Only the histoplasmin tests were positive. Histoplasma capsulatum was isolated from the parent's tissues obtained at autopsy and from two soil samples collected from the fertilized flower beds.

The authors urge that a provisional diagnosis of histoplasmosis be considered in all acute respiratory infections. Since an effective antimicrobial, amphotericin B, is now available, prompt diagnosis becomes urgent so that therapy can be initiated in time. The public health hazards of chicken habitats and manure are emphasized.

An Evaluation of Tuberculosis Case Finding by Tuberculin Testing and Some Observations of Histoplasmin Sensitivity Among Young School Children.—The authors present a review of observations made on tuberculin and histoplasmin skin tests performed yearly on kindergarten children in Kansas City over a 10-year period (1947-1957). During this time, 29,634 white children and 6,369 Negroes were tested and the over-all tuberculin sensitivity rate among Negroes was found to be almost twice that of whites (2.6% versus 1.5%).

Some of the more important facts derived from the study (as listed by the authors) are the following:

1. Tuberculin prevalence rates among children in the kindergarten show no tendency to fall over the 10 years of observation either in whites or Negroes, although the death rate from tuberculosis in Kansas City has fallen from 31.3 to 11.7 during the same 10 years.

2. The conversion rates to tuberculin observed in children who were nonreactors in kindergarten do not show a tendency to fall during the seven years of observation.

3. Use of the tuberculin test for obtaining index children whose contacts form a special risk group for extensive follow-up study not only gives a better yield of tuberculosis cases than mass roentgenography, but at the same time decreases the total exposure of a population to ionizing radiation.

4. The yield of active tuberculosis cases found by follow-up study of contacts of children who are converters was not greater than that found by follow-up study of children who were tuberculin reactors on the first test in kindergarten or first grade.

5. The cost of finding a case of tuberculosis by the methods of this study is approximately the same as for the mass roentgenographic method.

Archives of Disease in Childhood, London
Abstracted by R. Janet Watson, M.D.

33, No. 170 (Aug.) 1958

Paediatrics in Western Nigeria. Malcolm Macgregor.—p. 277.
Phlyctenular Conjunctivitis in African Children. Harry Stein and Ida Freiman.—p. 292.
Hormone Excretion in Precocious Puberty in Girls. R. D. Bulbrook, F. C. Greenwood and A. H. Snaith.—p. 293.
Urinary Excretion of 17-Ketosteroids in Children. Margaret Prout and A. H. Snaith.—p. 301.
The Urinary Excretion of 17-Hydroxysteroids in Children. R. Gardner and A. H. Snaith.—p. 305.
The Prognosis in Juvenile Obesity. A. G. Mullins.—p. 307.
Diabetes Insipidus Following Tuberculous Meningitis. John Lorber.—p. 315.
Diabetes Mellitus in a Child Showing Features of Refsum's Syndrome. J. B. Heycock and J. Wilson.—p. 320.
The Post-Natal Weight Loss of Babies Born to Diabetic and Non-Diabetic Women. James W. Farquhar and Stanley A. Sklaroff.—p. 323.
Jaundice and Infantile Diarrhea. R. G. F. Parker.—p. 330.
* Congenital Spherocytosis in Infancy. David Burman.—p. 335.
Congenital Heart Disease in One of Identical Twins. H. Everley Jones.—p. 342.
The Electrocardiographic Recognition of Ventricular Hypertrophy in Congenital Cardiovascular Disease During the First Year of Life. J. S. Oldham.—p. 346.
The Differential Diagnosis of Rheumatic Fever. Hallidie-Smith and Bywaters.—p. 350.
A Small Outbreak of Neonatal Meningitis in a Maternity Unit. Eric McKay and John Smith.—p. 358.
Neonatal Perforation of the Colon. Leonard Haas.—p. 362.
Bilateral Pulmonary Agenesis. A. E. Claireaux and H. P. Ferreira.—p. 364.
Atresia of the Oesophagus with Common Tracheo-Oesophageal Tube. R. G. Welch and O. A. N. Husain.—p. 367.
Psychogenic Megacolon in Children: The Implications of Bowel Negativism. Philip Pinkerton.—p. 371.

33, No. 171 (Oct.) 1958

Severe Infantile Hypercalcaemia with Special Reference to the Facies. M. C. Joseph and D. Parrott.—p. 385.
Congenital Absence of the Intrahepatic Bile Ducts. Leonard Haas and Richard H. Dobbs.—p. 396.
* Replacement Transfusion as a Means of Preventing Kernikterus of Prematurity. V. Mary Crosse, P. G. Wallis and Anna M. Walsh.—p. 403.
Serum Transaminase Variations in Childhood. Paolo Tolentino and Marcella Rossi.—p. 409.
A Test for Coeliac Disease. W. W. Payne and V. Jenkinson.—p. 413.
A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. Part I. Introduction. Part II. Physical Development. Cecil Mary Drillien.—p. 417.
Pancreatitis in Young Children. J. Collins.—p. 432.
Herpes Zoster Ophthalmicus in Children. S. M. Tucker.—p. 437.
Observations on the Bromide Partition Test in the Diagnosis of Non-Purulent Meningitis. V. S. Nicol and H. T. Fawns.—p. 440.
Pneumatosis Intestinalis in Chinese Children. C. S. Muir.—p. 445.
Physical Development of Schoolgirls in Upper Burma. C. V. Foll.—p. 452.
The Prevalence of Dental Caries in Relation to Maturity. J. N. Mansbridge.—p. 455.
Familial Dysautonomia. T. McKendrick.—p. 465.
Autopsy Findings in a Case of Pituitary Dwarfism. A. T. Sandison.—p. 469.
* Insufficient Glucuronide Formation in the Newborn and Its Relationship to the Pathogenesis of Icterus Neonatorum. M. Vest.—p. 473.
The First Arch Syndrome. J. McKenzie.—p. 477.

Congenital Spherocytosis in Infancy.—Dr. Burman reports the occurrence of congenital spherocytosis in identical twins and summarizes 41 reported cases under the age of one year. His two cases had neonatal jaundice, developed an anemia at 3 weeks of age requiring several subsequent transfusions, and were splenectomized at 9 and 11 months of age with excellent results. Neonatal jaundice was present in 23 cases, 2 of which developed kernicterus, and 3 received one or more exchange transfusions. Jaundice after the neonatal period was present in only six cases and was never a prominent symptom. Anemia was present in 38 cases, but did not appear before one week of age. The spleen was enlarged in 36 cases. Reticulocytosis, spherocytosis, and increased osmotic fragility were characteristic features of the blood picture. Splenectomy was performed in 27 cases, in 2 cases at the age of 3 and 5 days.

The author found that there were 10 instances of serious infection occurring after splenectomy and 4 deaths in this age group, and concludes that splenectomy be postponed until after infancy because of the risk of infection. He suggests that neonatal jaundice should be treated by repeated exchange transfusions and the anemia of infancy by simple blood transfusion.

Replacement Transfusion as a Means of Preventing Kernikterus of Prematurity.—The authors determined the bilirubin levels in the first eight days of life of 1,320 premature babies during the two-year period from July 1, 1955 to June 30, 1957. Exchange transfusion was undertaken in 92 babies (8.4%) whose bilirubin had reached 18-20 mg. % or was rising so

rapidly that it would probably have reached this level before the next morning. Cases of hyperbilirubinemia due to hemolytic disease were excluded from the study. Of the transfused babies, 19.6% required more than one transfusion. There were two deaths in the 92 babies who received 115 transfusions, but only one of the deaths could be attributed to the effect of the transfusion.

Most of the transfusions were performed on the fifth day of life, the earliest on the third day, and the latest on the seventh day. Five of the babies developed signs of kernikterus later in life; all of these had a bilirubin value over 22 mg. % before the first exchange transfusion. The authors were able to follow 83 of the 90 surviving babies to the age of one year. They conclude that replacement transfusion is the best way of preventing the kernikterus due to hyperbilirubinemia of prematurity at the present time.

Insufficient Glucuronide Formation in the Newborn and Its Relationship to the Pathogenesis of Icterus Neonatorum.—It has been demonstrated that the conjugation of a substance like *p*-aminophenol with glucuronic acid is catalyzed by an enzyme system in the microsomes of the liver and requires uridine diphosphate glucuronic acid (UDPGA) as the glucuronide donor. The enzymatic formation of bilirubin glucuronyl seems to involve the same system. The author used acetanilide (Antifebrin), 10 mg/kg., to assess glucuronide formation in 94 premature, full-term infants, and older children at the Children's Hospital, Basel, Switzerland. In adults and older children 80% of the compound is excreted as N-acetyl-p-aminophenol-glucuronide in the urine in 24 hours or less, whereas newborn, and especially premature, infants only eliminate a few small percentage in 24 hours. Even in 48 hours the total excretion in newborn infants amounts to only about 10% or less. Within the first weeks of life the power to conjugate glucuronic acid steadily increases to normal function by the age of 3 months.

The author eliminated insufficient excretory capacity of the kidneys as a possible cause by a calculation involving the known PAH clearance of the newborn, and concluded that the cause of the low glucuronide excretion was the inability of the newborn liver to conjugate glucuronic acid. Bilirubin determinations were also done in these babies, and an inverse relationship between the glucuronide excretion and bilirubin concentration was demonstrated. It is demonstrated that this insufficiency in the formation of glucuronides by the liver might be regarded as the underlying cause of icterus neonatorum.

A. M. A. Archives of Internal Medicine, Chicago

Abstracted by Philip N. Jones, M.D.

101, No. 3 (March) 1958

* The Effect of Therapeutic Mobilization on Hypercalciuria Following Acute Poliomyelitis. Fred Plum and Marcella F. Dunning.—p. 528.

Thyroxin and Triiodothyronine in Excessive Dosage to Euthyroid Humans. W. H. Beierwaltes and G. E. Ruff.—p. 569.

Movements and Forces of the Human Heart. J. R. Norman and T. R. Harrison.—p. 582.

Leptospirosis (Ballum) Contracted from Swiss Albino Mice. H. G. Stoenner and D. Maclean.—p. 606.

Heart Involvement in Infectious Mononucleosis. M. Fish and H. R. Barton.—p. 636.

Poliomyelitic Paralysis of Deglutition: Upper Esophageal Achalasia. Dag Scott.—p. 655.

* Jaundice and Bilirubin Metabolism. Rudi Schmid.—p. 669.

101, No. 4 (April) 1958

Comparative Clinical and Biochemical Effects of the Dextro- and Levo-Isomers of Thyroxine. Paul Starr.—p. 722.

Hemoglobin C-S Disease Complicated by Paracolon Osteomyelitis. Herbert W. Lohmuller and John F. Marshall.—p. 761.

* Treatment of the Deep Mycoses. John J. Procknow and Clayton G. Loosli.—p. 765.

101, No. 5 (May) 1958

* A Twenty-Year Appraisal of BCG Vaccination in the Control of Tuberculosis. Joseph D. Aronson, Charlotte F. Aronson, and Helen C. Taylor.—p. 881.

* Hereditary Pherocytosis. William F. Denny, Robert M. Bird and Merlin K. DuVal.—p. 894.

The Relationship of Abnormal Vascular Responses to Retinopathy and Neuropathy in Diabetics. Jörn Ditzel, Lynn Sargeant, and William B. Hadley.—p. 912.

Chronic Uremia Due to Polycystic Renal Disease Treated with the Artificial Kidney. S. Nakamoto and W. J. Kolff.—p. 921.

The Significance of Nonesterified Fatty Acids in Plasma. Vincent P. Dole.—p. 1005.

102, No. 1 (July) 1958

Serum Magnesium in Renal Diseases. William O. Smith and James F. Hammarsten.—p. 5.

Clinical and Histologic Spectrum of Pyelonephritis. George E. Schreiner.—p. 32.

* Familial Mediterranean Fever. Harry Heller, Ezra Sohar, and Libby Sherf.—p. 50.
* The New ECHO Viruses and Their Role in Human Disease. Dorothy M. Horstmann.—p. 155.

102, No. 2 (Aug.) 1958

Meningitis Due to Mima Polymorpha. Herbert L. Fred, Terry D. Allen, Herman L. Hassel, and Charles F. Holtzman.—p. 204.
* Infectious Diseases. Herbert A. Reimann.—p. 217.

Jaundice and Bilirubin Metabolism.—This is an excellent short review article dealing with the newer concepts of bilirubin metabolism. The explanation for the immediate and indirect van den Bergh reaction has been explained in various ways, but experimental evidence supporting various theories has been inconclusive. It has most commonly been taught that the indirect bilirubin reaction represents bilirubin that has been attached to a protein fraction and that the immediate direct van den Bergh reaction represents bilirubin that has been broken down in the liver into the so-called bilirubinate. The recent discovery that in the bile bilirubin is excreted as a conjugated glucuronic acid has brought some clarification to this whole problem. According to this newer concept which is being generally accepted, water-insoluble free bilirubin released from the reticuloendothelial cells is transported in the plasma by means of attachment to the proteins, mainly albumin. For excretion this unconjugated bilirubin is then converted by the liver to the water-soluble glucuronide. This finding that the excreted bilirubin is converted to a conjugated and more water-soluble form is not surprising in view of the fact that many other metabolytes have a similar fate in the liver. The process of conjugation is undoubtedly of enzymatic nature. In vitro experiments have shown that bilirubin glucuronide formation has been demonstrated and that the enzyme system present is in the liver microsomes.

Comment: This is an excellent review article written by an authority in this field and should be read by those interested in the mechanisms of jaundice or by anyone responsible for teaching of students or house officers.

The Effect of Therapeutic Mobilization on Hypercalciuria Following Acute Poliomyelitis.—Hypercalciuria and extensive osseous demineralization follow illnesses in which there is either flaccid or spastic muscle paralysis, and this appears to be true in patients with paralytic poliomyelitis whether there is only mild paralysis or whether there is extensive muscle denervation. The present study was undertaken to determine whether any artificial mobilization procedures could ameliorate or reverse the intensity and duration of the hypercalciuria among severely paralyzed subjects. Thirty-seven patients were studied and the following controlled mobilizing procedures were undertaken: rocking bed, tank treatment, sitting, standing, crutch-walking, and finally actual walking. These measures failed to introduce any immediate amelioration of the hypercalciuria and failed to shorten the duration of the hypercalciuria. The authors showed that any artificial measures short of the ability of walking itself had no immediate beneficial effects, nor was there any indication that these measures had any definite effect on the long-term pattern of excessive calcium wasteage.

Treatment of the Deep Mycoses.—During the past 10 years many new and promising antibiotic and chemotherapeutic agents have become available for the treatment of the deep mycotic infections, which consist of histoplasmosis, blastomycosis, coccidioidomycosis, actinomycosis, nocardiosis, cryptococcosis, moniliasis, aspergillosis, sporotrichosis, geotrichosis, and mucormycosis. This article consists of not only a detailed review of the current concepts of treatment of these infections but also a general review of the clinical manifestations. Each infection is discussed separately, and there is a comprehensive bibliography. Some of the new drugs available seem to be specific against a single fungus, while others show broad antifungal activity. Most, if not all, need further clinical trial before the extent of their effectiveness can be fully ascertained. Amphotericin B appears to meet the qualification of a broad-spectrum antibiotic against fungi. The authors point out that corticoids have no place in the treatment of chronic infections and that if used the patient may develop an overwhelming Candida infection. Only in the acute toxic phase of certain deep mycotic infections do they possibly have a place. Conventional supportive measures are still as equally important as the new drugs in the treatment of these infections. These fungal infections manifest a variety of signs and symptoms and should be considered in the differential etiology of both acute and chronic pulmonary infections, skin and mucous membrane lesions, and infections of the brain and blood.

Comment: This is an excellent review article and should be consulted for the detailed therapy when one encounters any one of these fungal infections.

Hereditary Spherocytosis.—The authors report two cases of hereditary spherocytosis which were studied during the "aplastic" crisis. These cases consisted of a mother and a 7-year-old son. In each case the crisis was characterized by profound anemia, reticulocytopenia, and depressed erythropoiesis in the bone marrow. It has been felt by some authorities that the spleen plays a role in the precipitation and maintenance of these "aplastic" crises. It was felt that these two patients could be considered as being a control for each other. The mother, therefore, had a splenectomy on the sixth day of the crisis, and the son was allowed to follow the normal course of the crisis. In the mother immediately after surgery there was the expected fall in serum bilirubin and the myeloid and megakaryocytic activity responded to the splenectomy in the expected fashion. However, there was no dramatic change in the degree of erythroid activity in the bone marrow or the level of the circulatory reticulocytes. As in her son, these developments made their appearance between the 9th and 14th days after the onset of the crisis. It was concluded that the splenectomy in the mother's case did not influence the duration of the "aplastic" crisis. On the basis of these findings the causative role of the spleen and the precipitation and maintenance of the "aplastic" crisis is questioned.

A Twenty-Year Appraisal of BCG Vaccination in the Control of Tuberculosis.—Although more than 100,000,000 persons have received BCG vaccine since 1921, skepticism remains, particularly in the United States, as to its protective value against tuberculosis. In an attempt to appraise, under field conditions, the protective value of BCG vaccine in the control of tuberculosis, an investigation was undertaken to study BCG vaccine among eight different Indian tribes living in five widely separated geographical areas. During the early years of this study economic conditions were uniformly low, housing conditions poor, and the morbidity and mortality from tuberculosis was reported as being high. Tuberculin-negative school and preschool children grouped by age and sex were divided by alternation into two groups. A group of 1,551 received an intracutaneous injection of BCG vaccine, while a group of 1,457 received an intracutaneous injection of isotonic sodium chloride and served as controls. In 1956, 20 years after the study was started, the areas were revisited and 99.7% of the vaccinated and 99.4% of the controls were accounted for. Among the vaccinated tuberculosis was responsible for 12.5% of all deaths, while among the controls tuberculosis was responsible for 45.3% of all deaths. In the control group the percentage of death from tuberculosis among females was twice as great as among males, but in the vaccinated group the same percentage of both sexes died of tuberculosis. Thus it would seem that the value of BCG vaccination, in this study at least, has been rather definitely established. However, in view of the rapid and marked decrease in the occurrence of tuberculosis in the United States, it would appear inadvisable to vaccinate the general population with the vaccine. Rather it is recommended that the BCG vaccine should be given to tuberculin-negative doctors, medical students, and nurses, who are exposed to tuberculosis; all hospital and laboratory personnel whose work exposes them to tubercle bacillus; persons who are unavoidably exposed to infectious tuberculosis in the home and hospitals and prisons and other custodial institutions; tuberculin-negative children and certain adults considered to have inferior resistance and living in communities in which tuberculosis mortality rate is unusually high.

The New ECHO Viruses and Their Role in Human Disease.—The authors present a review of the newest members of the enterovirus group, which have been designated as ECHO viruses. They point out that this is a rapidly growing family of some 20 agents, and that they are common inhabitants of the human intestinal tract, particularly in the summer time. They appear to be responsible for certain mild febrile illnesses, diarrheal syndromes, and occasional aseptic meningitis. They appear also to be present in many people, giving rise to inapparent infections. They have been associated also with several widespread epidemics both in Europe and the United States in which a rubella-like rash has been a prominent feature. These viruses have been isolated frequently in the last several years from human excreta, and their discovery actually has been a biproduct of tissue culture tests for the presence of polio viruses. They do not appear to produce any disease in the usual laboratory animals, and until recently it was felt that they were probably nonpathogenic for man. However, their relationship to disease is gradually becoming apparent.

Familial Mediterranean Fever.—The authors have described a new disease entity, which they have termed "familial Mediterranean fever." They described the clinical picture and laboratory findings of this syndrome in some detail. In brief, it is characterized by recurrent attacks of fever with painful manifestations of the abdomen, thorax, joints, and skin. It appears to be chronic and to have a cyclic nature. Patients have no difficulty between bouts of pains, which occur in various parts of the body. The authors reported some 74 new cases, which were seen personally by them, and they were able to cull from the literature 179 examples of this syndrome, which has gone by many different names. These patients previously have most often been described as examples of so-called "periodic disease." In studying their cases the authors were able to point out a rather definite hereditofamilial pattern, and it would appear that this syndrome occurs only among the ethnic groups of Mediterranean stock, particularly Jews and Armenians. They have also pointed out that the course, as far as known, appears to be a relentless one, and there appears to be frequent renal involvement terminating in amyloidosis and death in a certain percentage of cases. Very little pathological material, however, has been available for study. Seventy per cent of the patients had their first symptoms before the age of 10 years, and practically all of the patients had some manifestations of this syndrome before the age of 20. No treatment has been of avail, and practically all forms of treatment have been tried. There are no characteristic laboratory findings. The erythrocyte sedimentation rate usually is increased during the attacks as well as between them. During the attacks the leukocyte counts occasionally ranged between 10,000 and 20,000.

Infectious Diseases.—Dr. Reimann has again reviewed the significant publications during the past year concerning the general field of infectious diseases. He has reviewed some 324 separate articles, and for those interested in this field it would be well worth the effort to look up this original article. It is obviously impossible to even attempt to abstract this review article, but certain points are worth comment. There appeared to be little evidence that there is more discriminant or restrained prescription of the prodigious amounts of manufactured antimicrobics. As one result, the problem of antimicrobic resistance acquired by Staphylococci and other bacteria has intensified. He points out that one in four prescriptions filled at pharmacies called for antimicrobics. Again it is pointed out that antimicrobics are of no value in the treatment of the great majority of infections, mainly those caused by viruses. The current trend of packaged combinations of antimicrobials, which are being prepared by manufacturers has drawn adverse comment. It is felt that there is no justification for giving these mixtures for the ordinary type of infectious diseases which call for an antimicrobial treatment. The one major exception, of course, would be tuberculosis. The problem of how effective the new poliomyelitis vaccine is in reducing the number of clinical cases has been open to a good deal of comment. There are rather widely varying reports in the literature. It is pointed out that the death rate in 1956 during the year that mass immunization was started was about the same as in 1938, 1942, and 1947, when the vaccine was not used. In the past few years, more than 65 "new" viruses have been isolated from man in addition to the 60 already dealt with in current textbooks. Many of them as yet are unassociated with disease, but these studies may lead to further discoveries about diseases whose cause is still unknown. The possibility of tuberculous dogs and cats serving as sources of infection in man was considered. Nine persons in contact with infected dogs were found to have had tuberculosis, and among pets owned by patients with active disease tubercle bacilli were present in the intestines of two dogs and two cats. The controversy about the value of BCG vaccine continues. In spite of objections by several authorities, a medical advisory committee has urged its use. There is agreement, however, that vaccination is desirable for infants and children in areas of high incidence, for persons unavoidably exposed to infection, and for family members exposed in tuberculous households.

British Medical Journal, London
Abstracted by Hugo M. Cardullo, M.D.

2, No. 5100 (Oct. 4) 1958

Breast and Nipple Pain in Early Stages of Lactation. Bruno Gans.—p. 830.
Salt Losing Otorrhea. S. C. J. Shortman and A. D. M. Smith.—p. 834.

2, No. 5101 (Oct. 11) 1958

Malaria and Prematurity in the Western Region of Nigeria. D. S. H. Cannon.—p. 877.
Antibiotics in Acute Tonsillitis and Acute Otitis Media. John Fry.—p. 883.

2, No. 5102 (Oct. 18) 1958

Case of Infantile Ulcerative Colitis. J. Coll and D. Lang Stevenson.—p. 952.

2, No. 5103 (Oct. 25) 1958

* Simple Clinical Hearing Tests for Very Young or Mentally Retarded Children. Mary D. Sheridan.—p. 999.
Conversion Testing of School Children After BCG Vaccination. K. Neville Irvine.—p. 1018.
Tuberculous Meningitis Following BCG Vaccination. M. R. Kerr and J. M. Dunbar.—p. 1019.

Simple Clinical Hearing Tests for Very Young or Mentally Retarded Children (from Author's summary).—A series of simple clinical auditory screening tests which have been found useful in the preliminary assessment of the everyday hearing of very young or mentally handicapped children is described. The material required (common household objects, toys, and pictures) is listed. A brief summary of normal speech development during the preschool years is given.

Bulletin of the Johns Hopkins Hospital, Baltimore
Abstracted by Thomas K. Oliver, Jr., M.D.

103, No. 3 (Sept.) 1958

The Relative Importance of Blood and Urinary Concentrations of Sulfonamide in the Treatment of Urinary Tract Infections. A Comparison of Sulfisoxazole (Gantrisin) and Sulfamethyoxy-Pyridazine (Kynex, Midicel) in Man and Rat. Bashir A. Zikria, Louis Lasagna, and William P. McCann.—p. 117.

Canadian Medical Association Journal, Montreal
Abstracted by H. M. Keith, M.D.

79, No. 5 (Sept. 1) 1958

* Methaemoglobinaemia in Infancy. J. G. Armstrong, J. B. J. McKendry, and K. W. Slemon.—p. 392.
* Repeat Anencephaly. J. U. Coleman.—p. 395.

79, No. 8 (Oct. 15) 1958

* Report of an Outbreak of Febrile Illness with Pharyngeal Lesions and Exanthem: Toronto, Summer 1957—Isolation of Group A Coxsackie Virus. C. R. Robinson, Frances W. Doane, and A. J. Rhodes.—p. 615.
The Canadian Association for Retarded Children. H. G. Dunn.—p. 661.

Methaemoglobinaemia in Infancy: Two Case Reports, One of the Congenital and One of the Acquired Variety of Methaemoglobinaemia.—The first case of congenital methemoglobinemia was reported in 1844, and 38 others subsequently documented. The authors report another case, as well as one of acquired methemoglobinemia. In the congenital form there is a deficiency of one of the reducing enzymes, coenzyme I (diphosphopyridine nucleotide) and as a result methemoglobin accumulates. Treatment consists of giving a reducing substance such as ascorbic acid or methylene blue. Criteria for distinguishing between congenital and acquired varieties of methemoglobinemia are discussed.

Repeat Anencephaly.—Anencephaly is the commonest form of single monstrosity, 0.72 per 1,000 live births, but repeat anencephaly is uncommon. Both heredity and environmental causes have been proposed as etiologic. The probable basic pathologic picture is abnormal angiogenesis of the brain with failure in development of the neural tissue, due, in the reported case, to defective germ plasm. The author reports one case in which the mother had had three previous deliveries of anencephalic fetuses. The fourth child was shown by x-ray to be the same, and abdominal hysterotomy and sterilization were carried out.

Report of an Outbreak of Febrile Illness with Pharyngeal Lesions and Exanthem: Toronto, Summer 1957—Isolation of Group A Coxsackie Virus.—In the summer of 1957, in a Toronto suburb, there was an outbreak of a febrile illness, thought to be due to a Group A coxsackie virus. The latter was isolated from 71% of the patients and showed serological relationship to virus A 16. It was obtained from stool and from throat preparations, but not from the blood or vesical fluid.

The disease was characterized clinically by fever, the presence of pharyngeal ulcerative lesions, and a maculopapular and vesicular exanthem, which affected 60 patients. The illness was mild; admission to hospital was not necessary, and there were no sequelae. The incidence of the disease was highest in children aged 1 to 9 years. The details of the epidemiology, and of the virus studies are given.

Journal of the American Medical Association, Chicago
Abstracted by Don M. Hosier, M.D.

168, No. 4 (Sept. 27) 1958

Prolonged Intermittent Steroid Therapy for Nephrosis in Children and Adults. Kurt Lange, Edward Wasserman, and L. B. Slobody.—p. 377.

168, No. 7 (Oct. 18) 1958

Pediatrics in Transition. G. M. Wheatley.—p. 856.
* Serum Transaminase Activity in Neonatal Period. Simon Kove, Stanley Goldstein, and Felix Wroblewski.—p. 860.

Serum Transaminase Activity in Neonatal Period.—The patterns of serum enzyme activity for both glutamic oxalacetic transaminase (GO-T) and glutamic pyruvic transaminase (GP-T) that evolved from these studies appeared to have significant diagnostic implications in neonatal icterus, a syndrome in which the usual diagnostic procedures may be of no help and may actually be misleading.

Clinical and laboratory data were obtained showing that the differential diagnosis of neonatal icterus is facilitated by serial measurements of transaminase activity of the serum. In 63 normal newborn infants the GO-T activity levels ranged from 13 to 120 units; for the GP-T the range was 12 to 90 units. Physiologic hyperbilirubinemia in newborn infants did not affect the level of the GO-T and GP-T activity. Data from 15 infants with jaundice due to pathological conditions indicated that characteristic patterns of enzyme activity appear for each of the varied causes of neonatal icterus. In infants with extrahepatic infection and usually in those with hemolytic conditions the enzyme activity remained within the normal range. The authors state that serial determinations of serum transaminase activity in cases of neonatal icterus aid in the recognition of patients requiring surgery.

Journal of Pediatrics, St. Louis
Abstracted by Demetrius G. Traggis, M.D.

53, No. 4 (Oct.) 1958

Adrenogenital Syndrome Due to Congenital Virilizing Adrenal Hyperplasia. J. N. Etteldorf, Constantin Missirliu, and W. Fleischmann.—p. 389.
Learning Disabilities Associated with Lesser Brain Damage. H. E. Thelander, J. K. Phelps, and E. W. Kirk.—p. 405.
Group Dynamics in the Treatment of Epilepsy. S. H. Kamin, C. J. Llewelleyn, and W. L. Sledge.—p. 410.
The Bacteriological Diagnosis of Childhood Tuberculosis Using Bone Marrow and Peripheral Blood Aspirates. L. S. Kimsey.—p. 413.
Surgical Treatment of Some Pulmonary Conditions in Childhood. M. L. Cantlin, C. J. Rominger, and W. D. O'Sullivan.—p. 432.
A Terminology and Differential Diagnosis for Brief Seizures in Infants and Children, and the Definition of Petit Mal. E. H. Senz.—p. 441.
Prolapsing Trigonal Mucosa in Infant. R. R. Espinosa, R. L. Blanco, and V. Picornell.—p. 446.
* Prognosis in Legg-Perthes Disease. H. M. Broder.—p. 451.
Calculation of Nutritional Allowance for Infants and Children of the Basis of Body Surface. G. B. Stickler and D. Pinkel.—p. 464.
Education of Cerebral Palsied Children. B. E. Katz.—p. 467.
Ferrous Sulfate Poisoning. E. E. Amerman, M. A. Brescia, and F. Aftahi.—p. 476.
Incarceration of Meckel's Diverticulum in an Inguinal Hernia. A. H. Kline.—p. 479.
Familial Dysautonomia. H. E. Stadler.—p. 481.
Leptomeningitis Due to Gaffkya Tetragena. M. L. Perou, R. T. Fielding, and H. M. Nelson.—p. 484.
A Case of Malignant Sacrococcygeal Teratoma. E. M. McConnell.—p. 489.
The Children's Medical Center, Boston, Mass.—p. 494.
Mammalian Viruses and Rickettsiae: New Methods of Purification and Recovery. R. J. Blattner.—p. 503.

Prognosis in Legg-Perthes Disease.—The author reviews 208 cases of Legg-Perthes disease with the object of trying to find factors of prognostic importance which might aid in the correct treatment. He reviews the different ideas in the literature. Of 200 patients, 33% were first seen between ages 2.8 and 5 years, 50% between 6 and 9 years, and 17% between 10 and 14 years, 79.8% were male. The right side was involved slightly more frequently than the left, and 13% were bilateral. The authors used x-ray criteria for the determination of progress. Several charts are presented showing the following: 1. The milder the disease the better were the results. 2. The milder cases occurred in younger age groups. 3. The results tended to be worse with increasing age of child. 4. Those treated with bed rest and those allowed up (with non-weight-bearing) appeared to have about the same result. A

group treated by both methods showed poorer results. This author feels that keeping the patient ambulatory with non-weight-bearing is the preferable method, chiefly from the fact that the children are happier and have fewer behavior problems than those confined to bed.

Medical Journal of Australia, Sydney

Abstracted by George H. Lowrey, M.D.

1, No. 25 (June 21) 1958

These papers were presented at the Australasian Medical Congress (British Medical Association), Section of Pediatrics, Hobart, March 1 to 7, 1958.

Thirty Years of Juvenile Rheumatism. Laurence Hughes.—p. 872.

Failure to Thrive. N. S. Chalk, E. Turner, W. B. MacDonald, K. Campbell, S. E. L. Stening, M. Powell, H. L. Davis, H. S. Patterson, and S. F. McCullagh.—p. 872.

The Nephrotic Syndrome. R. H. Vines, K. Campbell, S. F. McCullagh, M. Powell, D. Hamilton, J. Matthews, and M. Luck.—p. 873.

Patent Ductus Arteriosus. D. Cohen, S. Williams, J. Matthews, C. J. Brown, R. Southby, and P. Dorney.—p. 874.

The Surgical Significance of Pulmonary Hypertension. N. A. Myers, L. W. Knight, A. E. Doyle, C. J. Officer Brown, P. Jones, and D. Cohen.—p. 875.

Neonatal Cyanosis. J. D. Matthews, K. Campbell, M. Powell, and W. B. MacDonald.—p. 876.

Steatorrhoea in Childhood. C. Anderson, R. Wall, and M. Powell.—p. 877.

Immunization in Pregnancy with Rh Haemolytic Disease of the Newborn. G. A. Kelsall, J. H. Colebatch, K. Campbell, and J. D. Matthews.—p. 877.

2, No. 2 (July 12) 1958

* The Chemotherapy of Tuberculosis in Infants: An Eight Year Follow-Up. Munro Ford.—p. 40.

2, No. 4 (July 26) 1958

The Absorption of Penicillin V in Children. Stanley W. Williams, A. G. Matthews, and H. K. Harcourt.—p. 117.

Survivorship in Neuroblastomatosis: Report of a Case with Commentary. Robert G. Woods.—p. 125.

2, No. 5 (Aug. 2) 1958

Exterior Gestation, Primitive Sleep, Enuresis and Asthma: A Study in Aetiology: Part I. John Bostock.—p. 149.

Salmonella Osteomyelitis in Infancy with a Case Due to Salmonella Newport Infection. D. C. Jackson.—p. 160.

2, No. 6 (Aug. 9) 1958

* Exterior Gestation, Primitive Sleep, Enuresis and Asthma: A Study in Aetiology: Part II. John Bostock.—p. 185.

2, No. 7 (Aug. 16) 1958

* A Laboratory Study of Laryngo-Tracheo-Bronchitis in Children in Melbourne (1956). Doris M. Graham.—p. 223.

2, No. 9 (Aug. 30) 1958

The Second Australian Example of Anti-S Associated with the MNSs Blood Groups. M. L. Verso and R. T. Simmons.—p. 286.

* Radiation Hazards to the Foetus. Lance Townsend.—p. 289.

The Role of the Pre-School Centre in the Teaching of Medical Students. D. C. Jackson.—p. 290.

The Chemotherapy of Tuberculosis in Infants: An Eight Year Follow-Up.—In Australia, prior to 1947, when no chemotherapy was used, the fate of children under the age of 2 years who were found to have a positive Mantoux reaction was bad. In a five-year follow-up period, 35% had died of tuberculosis and 31% had developed bone and joint complications. These figures are comparable to other studies throughout the world. Because of this poor prognosis the following study was undertaken. Forty children under 3 years of age were included in the group. Fourteen of these had only a positive Mantoux reaction. Eighteen had definite lung involvement, and eight had other evidence of tuberculosis infection. Treatment was continuous for six weeks. Thirty-four received streptomycin alone, averaging 0.5 gm. a day in divided doses. Five patients also received PAS. All patients were followed for at least eight years. Three patients could not be traced. Of the 37 patients followed, none had died at the end of the study period. Five, or 14%, had an exacerbation of their tuberculosis. Two developed tuberculosis meningitis, one tuberculosis of the hip, one cervical adenitis, and one bronchiectasis. The author concludes that primarily tuberculosis in small children should not be left to its natural course.

Exterior Gestation, Primitive Sleep, Enuresis and Asthma: A Study in Aetiology: Parts I and II.—This is an interesting and provocative discussion primarily concerned with enuresis and only occasionally discussing asthma. The author traces the evolution of the period

of gestation, pointing out that in animals who at birth must be relatively mature, as a matter of their own protection, are those with the longest period of gestation. Man is less mature at birth than many animals, and has a period following birth of approximately 8 to 10 months in which he is like many of the animals completing periods of gestation. In support of this, he points out that the sleep of the infant is the predominant behavior pattern and is not easily disturbed. This is related to enuresis, the author believes, because it is during this period that the abnormalities of micturation are established. In the study of enuretic children there was a constantly recurring pattern consisting of preoccupation by the parents in toilet training and difficulty in awakening the child from a deepened sleep. In several of their control studies under varying conditions, the enuretic child constantly was more difficult to awaken than the normal child, and often manifested conditions of being "half awake" or "asleep on his feet." In contrast to the control, the enuretic child often seemed to be less easily disturbed by outside stimulation; in fact, at times the stimuli seemed to drive him into still deeper sleep.

The author points out that in primitive societies and our own civilization a century ago, enuresis was either absent or much less of a problem. With the knowledge of germs and the quest for good hygiene, parents have become preoccupied and obsessed with cleanliness for their children and infants. Early and vigorous toilet training has resulted. This has often interfered with the sleeping pattern of the child. It is emphasized that in all children who become bed wetters other factors often play a part. The combined findings of the personality type of the mother and overstimulation of the infant are consistent ones except where organic causes of the enuresis are present.

A Laboratory Study of Laryngo-Tracheo-Bronchitis in Children in Melbourne (1956).—(Author's Summary) Fifty-eight cases of laryngo-tracheo-bronchitis were studied by virological and bacteriological methods. Attempts to isolate influenza virus failed, and serological tests did not show the incidence of influenza, psittacosis, "Q" fever, glandular fever or diseases associated with the development of cold agglutinins. The isolated bacteria were not homogeneous. Adenovirus Type 2 was isolated from one throat washing, and 31 patients had antibodies against adenoviruses. Current infection by Type 2 adenovirus was revealed in 2 out of 18 cases by a rise in specific antibodies. Thirteen out of eighteen patients showed previous infection with adenovirus Type 2, five with Type 3, and one with Type 7 (five showing dual infection), and four further patients with adenoviruses of unidentified type.

Radiation Hazards to the Foetus.—Because there has been much written about the dangers of radiation to children, Townsend studied the effects in utero. This was a retrospective study, and the author recognizes its limitations. The parents of 168 children who died of leukemia were questioned. These 168 constituted the vast majority of leukemic children in the area studied. Seven per cent of the mothers had had x-ray during their pregnancy. In the same area in any one year, approximately 1,000 infants are either still born or died within the first four weeks after birth. This figure reflects the hazards involved in labor. It is speculated that diagnostic x-ray examination would save many of these infants by supplying valuable information to the attending physician. The author concludes from these figures that we can neither prove nor disprove that x-rays in utero causes leukemia in children. X-radiation of the mother should be done with the utmost care to protect the fetus. It should not be a routine part of the mother's examination. However, when indicated, this type of examination would probably save more lives than it would cost.

Medizinische Klinik, Munich
Abstracted by Samuel Amberg, M.D.

53, No. 28 (July 11) 1958

* The Problem of Radiation Lead and Radiation Protection in Pediatric Roentgen Diagnosis. K. Hartung.—p. 1209.

53, No. 30 (July 25) 1958

The Nonspecific Inflammatory Diseases of the Nasopharynx in Childhood. R. Schröer.—p. 1311.

53, No. 31 (Aug. 1) 1958.

* Examination for Appendicitis in Young Children. L. Zorn.—p. 1339.

53, No. 32 (Aug. 8) 1958

* Chickenpox in Children with Epidemic Hepatitis. V. Krebda.—p. 1365.

53, No. 35 (Aug. 29) 1958

* A New Long-Acting Sulfonamide in Pediatric Practice. L. Brockhaus.—p. 1505.

53, No. 36 (Sept. 5) 1958

* The Use of Fructose in Modern Therapy. K. Stuhlfauth.—p. 1554.

53, No. 39 (Sept. 24) 1958

* Oral Oxytetracycline Medication in Pediatrics. R. R. von Paar and P. Schweier.—p. 1690.

53, No. 42 (Oct. 17) 1958

* Neuropathologic Investigations of the Stomach of Infants with Hypertrophic Stenosis of the Pylorus. H. Zimmermann.—p. 1811.
* Clinical Results with a New Diuretic Free from Mercury (Orpidan) in Children. H. Patzer.—p. 1826.
* Antibiotic Treatment of Dyspepsia of Infants. I. Klupsch.—p. 1829.

The Problem of Radiation Load and Radiation Protection in Pediatric Roentgen Diagnosis.—In about 3,000 determinations by the author the surface and gonad doses of x-rays from a four-valve apparatus were measured by means of condensation chambers and compared with postmortem determinations. The volume doses (radiated body volume) and relative volume (relation of radiated to nonradiated parts of body) are considered besides the radiation intensity on the skin. Special attention is given to the measurement of radiation to the gonads on application of the rays to other parts of the body. A system of radiation protection measures is described, permitting a significant reduction of radiation of skin and gonads on x-ray examination of children. The paper offers many interesting features.

Examination for Appendicitis in Young Children.—This short paper gives a description of examining the sitting child by placing the thumbs on the pelvis and the four fingers of the hands on the lower abdomen.

Chickenpox in Children with Epidemic Hepatitis.—Over a number of years 105 children with hepatitis or in early convalescence, without previous history of chickenpox, were exposed to chickenpox. In 73 of these chickenpox occurred. In 8 instances the disease was typical, in the other 65 it was atypical, the efflorescences appearing in one or two stages, rarely in three. They were scanty and in only a few cases purulent vesicles were seen; otherwise small papules predominated. Crusts formed only where vesicles had been or on scratching of the papules. The skin eruption persisted for three to seven days.

A New Long-Acting Sulfonamide in Pediatric Practice.—The preparation 153 (*p*-amino-benzolsulfonamido)-2 phenylpyrazol (Orisul, Ciba) has the advantage of prolonged activity. Smaller doses are required than of other sulfonamides, and it is only necessary to give it once a day by mouth in the form of tablets or as syrup. The dosage for infants is 0.5 gm., for young children 1.0 gm., and for schoolchildren 1.5 gm. The drug is well tolerated. It was given to 153 children with various infections, such as bronchopneumonia, infections of the upper respiratory tract, otitis media, Enterococcus dysentery, and infections of the urinary tract. The efficiency is about the same as that of other modern sulfonamides.

The Use of Fructose in Modern Therapy.—The review stresses the advantages of fructose administration over that of glucose in various diseases.

Oral Oxytetracycline Medication in Pediatrics.—Using a calcium complex of terramycin with various additions, two preparations were prepared, one of which could be given as drops and the other as syrup. The taste of these preparations was good. Drops are especially useful for ages up to 14 months. Depending on the severity of the disease 25-50 mg/kg. was the dosage, and the duration of treatment varied from about 9 to 13 days. The results with various infections corresponded with those reported in the literature. The treatment proved especially effective in cases of dysentery (Sonne) and Salmonella infections.

Neuropathologic Investigations of the Stomach of Infants with Hypertrophic Stenosis of the Pylorus.—It was possible to obtain stomachs on postmortem examination of four infants 11 to 20 hours after death. The infants, aged 26 days to 4½ months, had pylorospasm. Suitable control stomachs were also examined. The changes of the hypertrophic plyoric muscles confirmed previous observations. Special attention was paid to the histologic lesions of the nervous system, including the terminal reticulum. The importance of determining the argentophilic components is emphasized. Degenerative lesions were seen in the ganglion cells of the Auerback and Meissner plexus. The neurofibrils present lesions of various intensity, the

fibers of the terminal reticulum were damaged severely. These changes occur in all parts of the stomach but particularly in the pyloric region. The etiology of hypertrophic stenosis of the pylorus is discussed and it is concluded that a primary disorder of innervation seems to be responsible.

Clinical Results with a New Diuretic Free from Mercury (Orpidan) in Children.—Orpidan (commercial, L. Heumann, Nürnberg) is N-*p*-chlorophenyl 2-4-diamino-s-triazin. Its diuretic effect in animal experiment exceeds that of Diamox considerably. The drug was given to children orally. In adults the daily dosage is 1 to 3 mg/kg., in infants it was 4-6 mg/kg. It proved beneficial, particularly in cardiac edema and fluid accumulations. It was given in a case of lipoid nephrosis and in a case of nephrotic syndrome, with prompt release of the edema. The number of cases is not sufficient for a good evaluation.

Antibiotic Treatment of Dyspepsia of Infants.—Bacteriostatic and bacteriocidal activity of neomycin on dyspepsia colon bacilli was tested. A combination of neomycin and bacitracin called "Nebacetin," was given to dyspeptic infants under bacteriological control of the stool. The results are graded as very satisfactory. The bacitracin prevents Staphylococcus enteritis. The daily dosage was 33 mg. neomycin per kilogram and 2,500 units of bacitracin in tablet form divided in four parts. It was given for four days. When treatment of dyspeptic infants is carried out at home, the use of antibiotics is required only in severe cases with toxic symptoms. In the hospital all infections with pathogenic colon bacilli are given antibiotic treatment to prevent the spread of infection.

Metabolism, New York
Abstracted by S. A. Kaplan, M.D.

7, No. 3 (May) 1958

Primary or Idiopathic Diabetes Insipidus. A System Disease. H. Blotner.—p. 191.
The Biochemical Basis of Mental Dysfunction. R. W. Lippman, T. L. Perry, and S. W. Wright.—p. 274.

7, No. 4 (July, Pt. 1) 1958

Nitrogen-Retaining Properties of 17-Ethyl-19-Nortestosterone. F. J. Saunders and V. A. Drill.—p. 315.

7, No. 4 (July, Pt. 2) 1958

* Symposium: Biological and Clinical Investigations of Newer Hydrocortisone Analogs. Ed. L. J. Soffer and R. H. Orr.—p. 383.

7, No. 5 (Sept.) 1958

Clinical Studies on the Diuretic Effect of Clorothiazide. G. J. Magid and P. H. Forsham.—p. 589.

Symposium: Biological and Clinical Investigations of Newer Hydrocortisone Analogs.—The therapeutic efficiency of adrenocortical hormones in a wide variety of diseases has all but revolutionized certain phases of clinical medicine. However, the use of cortisone and Cortisol (hydrocortisone) has not been without its drawbacks, and the "side-actions" of these preparations have been worrisome and, in some cases, definitely harmful. As a result, the organic chemists have concentrated their efforts on synthesizing chemical analogues of cortisone and hydrocortisone in the hope that some of the new compounds might still have the anti-inflammatory properties of the parent compounds while possessing fewer side-effects.

In 1955 Bunim et al. first reported on the clinical use of prednisone and prednisolone in patients with rheumatoid arthritis. In these compounds a double bond is introduced between C_1 and C_2 of cortisone to produce prednisone, and in the same position in hydrocortisone to produce prednisolone. The newer preparations were found to have four times the anti-inflammatory potency of the parent compounds, and as a result the dosage could be reduced fourfold. The salt-retaining and potassium-losing properties of the newer compounds (especially at the lower dosage level) were found to be slight, but toxic effects still occurred.

Since the introduction of prednisone and prednisolone other substituted steroids have been synthesized with varying degrees of potency, although many of these do not yet have any clinical application. For example, the introduction of fluorine in the 9α position will increase the salt-retaining properties by 300-900 times. Similarly, introduction of a methyl group at C_6 results in a considerable increase in both mineralocorticoid and anti-inflammatory activity. The accompanying table summarizes the comparative effectiveness of the various synthetic and natural steroids.

Comparative Effectiveness of Various Steroids

Hormonal Agent	Anti-Inflammatory Activity	Average Initial Daily Oral Dose, Mg.	Average Maintenance Daily Oral Dose, Mg.	Sodium-Retaining Effect	Potassium Diuretic Effect	Effect on Protein and Carbohydrate Metabolism	Inhibition of Endogenous ACTH
Cortisone	1	200-300	50-100	1	1	1	1
Cortisol	1-1.25	200-300	50-100	1.25	1	1.25	1.25
Prednisone	3-5	40-60	10-25	None	Slight	3-5	3-5
Prednisolone	3-5	40-60	10-25	None	Slight	3-5	3-5
6-Methyl prednisolone (Medrol)	3-5	32-48	8-24	None	Slight	4-6	3-5
2-Methyl cortisol	4-5	30-50	5-20	80-100	5-10	4-5	?
Desoxycorticosterone acetate	0	—	—	30-50	5	0	0
Aldosterone	0-?	—	—	300-900	10-25	0	0?
9α-Fluorocortisol	10-15	8-12	4-6	300-900	10-25	10-15	10-15
9α-Fluoroprednisolone	—	—	—	300-900	10-25	50	?
2-Methyl 9α-fluorocortisol	—	—	—	1,000-2,000	?	9	?
9α-Fluoro-16-hydroxy prednisolone (triamcinolone, Aristocort)	3-5	32-48	8-24	None	?	4-6	3-5

In this table some properties of the newer derivatives are compared with those of cortisone by assigning to the latter the arbitrary value of 1.

Of greatest clinical interest at the present are the two compounds, 6 methylprednisolone (Medrol) and 9-α-fluoroprednisolone (triamcinolone, Aristocort). These two new agents have been used in the treatment of the following diseases: The adrenogenital syndrome, hay fever, bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, a variety of dermatoses, ulcerative colitis, leukemia, acquired hemolytic anemia, idiopathic thrombocytopenic purpura, anerythrogenic anemia, bone marrow hyperplasia, lymphosarcoma, and acute and chronic uveitis.

As with all new preparations the final judgment on whether these are superior to prednisone and prednisolone will have to await the test of time. At present it appears that a slightly lower dosage of these compounds may be effective in the treatment of those diseases which respond to treatment with the older steroids. It does not appear, however, that a new milestone in therapeutics has been reached with the introduction of these new preparations for clinical use.

Monatsschrift für Kinderheilkunde, Berlin
Abstracted by Hans Hartenstein, M.D.

106, No. 3 (March) 1958

Proceedings of the 56th Meeting of the German Society of Pediatrics in Duesseldorf, Sept. 16-18, 1957.

Topic 1. Physiology and Pathology of Fluid Metabolism in Infancy:

Posterior Pituitary and Adrenal Cortical Hormones During Early Infancy and Their Relationships to the Regulation of Water Metabolism. H. Heller.—p. 81.

The Development of the Neurosecretory Regulation of Water Metabolism in the Infant. H. Rodeck.—p. 82.

Fluid Metabolism in the Infant. H. Hungerland.—p. 90.

Renal Factors in the Genesis of Body Water Loss with Primary Salt Deprivation. E. Kerpel-Fronius, J. Voenoeczky, and J. Szigethy.—p. 99.

Hormonal Regulation of Water Metabolism. J. R. Bierich and R. Gruettner.—p. 101.

The Functional Immaturity of the Kidney of the Infant as a Limiting Factor in Artificial Feeding. Helga Stolley and W. Droese.—p. 104.

The Significance of Oncotic Pressure in Serum on Fluid Distribution in the Extracellular Space. R. Schulz.—p. 107.

Recent Results and Methods Regarding the Mechanism of Urine Concentration. K. H. Jarausch and K. J. Ullrich.—p. 108.

Influence of Water Metabolism on Circulation in Early Life. Fritz Graser.—p. 111.

The Effect of Fractionated Vitamin D₂ Supplementation on Various Renal Functions. M. Loudon and E. Zweymueller.—p. 112.

Miscellaneous Topics:

Angiocardiography in Children with Cerebral Disturbances. K. Kundratitz, E. Klausberger, and E. Zweymueller.—p. 113.

Anesthesia with Steroids. Schaper and Kosenow.—p. 117.

The Occurrence of Poliomyelitis Neutralizing Antibodies in the Blood of Infants and Young Children in Würzburg and Vicinity. W. Bommer.—p. 119.

Emergency Therapy with Steroids. F. Souchon.—p. 118.

Treatment of Very Severe Burns with "Vegetative Slumber". H. Kaloud.—p. 121.

Topic 2. Industrial Treatment of Food and Its Medical Significance.
Industrial Treatment of Food as a Problem for the Nutrition Physiologist. H. D. Cremer.—p. 123.
Industrial Treatment of Food and the Physician. Kuer Schreier.—p. 130.
Proteins in Infant Foods After Industrial Treatment. R. Koch.—p. 137.
Conservation of Milk in Infant Feeding. H. Ewerbeck.—p. 137.
Freeze-Drying as a Natural Method of Conservation of Human Breast Milk. Carl-August Sager.—p. 138.
Significance of Colonic Bacteria on the Fat Content of Feces in Healthy and Dyspeptic Infants. Walter Marget and Franz Debatin.—p. 141.
Miscellaneous Topics:
Thymus Enlargement in Children. Toshio Otani.—p. 143.
Topic 3. The Kidney of the Child and Its Diseases:
Modern Concepts of the Physiology of the Nephron. G. Fanconi.—p. 145.
Thoughts and Methods Regarding Clearance Tests. F. H. Dost.—p. 147.
Practical Results of Clearance Studies. F. K. Friederiszick.—p. 149.
Experimental Nephritis in Young Animals. Gerhart Erdmann.—p. 151.
Pathogenesis of Acute Diffuse Glomerulonephritis. Werner Catel.—p. 155.
Current Status of Therapy for Lipoid Nephrosis. G. Fanconi.—p. 159.
Nephrosis and the Adrenal Gland. W. Falk.—p. 161.
Disturbances in the Reabsorption of Amino Acids and Sugar by the Proximal Tubules. H. Bickel.—p. 162.
Secondary Disturbances of the Proximal Tubules. P. Durand.—p. 165.
Disturbances in the Mechanism of Tubular Phosphates. Pierre Royer.—p. 167.
True Vitamin D-Resistant Rickets. W. Swoboda.—p. 168.
Renal Diabetes Insipidus. F. Linneweh.—p. 169.
Renal Function and Urine Ionogram. H. Hungerland.—p. 171.
Regulation of Acidosis and Alkalosis. W. Droese.—p. 172.
Hypercalcemia and Renal Function. G. Fanconi, Thomas Stapleton, and William McDonald.—p. 175.
Treatment of Anuric Nephropathies. E. Gautier.—p. 176.
Renal Function in Pyelonephritis. Rolf Zetterstroem.—p. 178.
Pyelonephritis and Hydronephrosis as Causes of Tubular Disturbances. J. Jochims.—p. 180.
Oxalosis as a Cause of Renal Dwarfism. G. De Toni.—p. 185.
Impaired Growth Due to Occult Malformation of the Uretera Without Hydronephrosis. A. Loeschke.—p. 187.
Nephrocalcinosis. H. Loehr.—p. 188.
Nephrosis in the Newborn. L. Hjelt and N. Hallmann.—p. 190.
Indications for the Use of Conteben in the Nephrotic Syndrome in Childhood. Egon Werner.—p. 192.
Treatment of Nephrosis with Kempner's Rice Diet. Dietrich Vogt.—p. 194.
Indirect Renal Clearance Using Inulin and PAH Half-Times. V. Dietel and H. Polster.—p. 197.
Renal Electrolyte Excretion and the Determination of Certain Tubular Functions. A. Rosenkranz.—p. 199.
Epidemiological Observations on Nephritis in Childhood. H. Gutheil.—p. 200.
Bacteriological Diagnosis of Urinary Tract Infections. E. Zapp.—p. 201.
Two Cases of Galactosemia. B. S. Schultze-Jena.—p. 203.

106, No. 4 (April) 1958

Genetic-Clinical Studies of Abnormal and of Brain-Damaged Children.
1. Introduction & Statement of Problems. Walter Hirsch.—p. 209.
2. Carotene & Vitamin A Metabolism. Walter Hirsch and A. Mex.—p. 210
3. Paper Chromatography. Walter Hirsch and H. J. Belitz.—p. 212.
4. Electroencephalography. Walter Hirsch, W. Goetze, and St. Kubicki.—p. 213.
5. Finger Prints and Palmar Dermatoglyphics. G. Geipel and Walter Hirsch.—p. 215.
Bronchoscopic Results in Primary Tuberculosis in Infants and Children. K. von Windheim.—p. 223.
Differential Diagnosis of Thalassemia Minor and Other Hemolytic Diseases in Infancy. P. Sachtleben.—p. 228.
The Origin of Hypoproteinemia in Infants with Leiner's Disease. P. Ferencz and D. Boda.—p. 234.
* Poliomyelitis Antibodies in Infancy. W. Anders.—p. 236.
Adiposity and Polyphagia in Leukemia. F. Allies.—p. 237.
Review Article: Psychology, Psychopathology and Psychotherapy. Heinz Spiess.—p. 239.

Poliomyelitis Antibodies in Infancy.—Infants living in West Germany ranging in ages between birth and 2 years were examined for the presence of antibodies for poliomyelitis. It was found that 12.7% of newborn infants had no antibodies. After nine months 73.3% had no antibodies. During the first two years of life 8- and 9-month-old infants were the lowest group possessing neutralizing antibodies against poliomyelitis.

New England Journal of Medicine, Boston
Abstracted by Demetrius G. Traggis, M.D.

259, No. 14 (Oct. 2) 1958

Clinical Experiences with Kanamycin. P. A. Bunn and A. Baltch.—p. 659.
* Anomalous Artery in Intralobar Bronchopulmonary Sequestration: Report of Two Cases Demonstrated by Angiography. F. P. Gerard and H. A. Lyons.—p. 662.
A Widespread Epidemic of Typhoid Fever Traced to a Common Exposure. W. A. Neill, J. D. Martin, E. A. Belden, and W. Y. Trotter.—p. 667.

Anomalous Artery in Intralobar Bronchopulmonary Sequestration: Report of Two Cases Demonstrated by Angiography.—Intralobar bronchopulmonary sequestration of the lung refers to the association of a congenital cyst of either lower lobe associated with an anomalous artery arising from the aorta either above or below the diaphragm. The authors present two cases. One was in a 58-year-old man who entered with fever, chills, cough, and had a mass in the right lower lobe which persisted. Bronchoscopy was normal. Bronchogram showed no filling of the abnormal segment. Angiocardiography revealed an anomalous artery arising from the abdominal aorta, perforating the diaphragm, and supplying the mass. At operation the mass was removed. Drainage was by a systemic vein. The second case was a 6½-year-old girl who had had several episodes of pneumonia in the same area ever since birth (birth weight 4 lb. 5 oz.). At birth x-ray revealed a cystic mass surrounded by pneumonitis each time but the cystic mass persisted. Bronchogram indicated incomplete filling of the posterior basilar segment on the left. An aortogram revealed one large and several small anomalous arteries arising from the thoracic aorta. Surgery was curative. Venous drainage was systemic. The authors give a brief history of the condition and discuss its importance and diagnosis. It is a cause of chronic lung disease with recurrent bouts of acute infection associated with a persistent x-ray abnormality. Often no bronchus enters the area. The mass may consist of normally differentiated lung tissue, or a system of branching bronchi, or one or more bronchogenic cysts, or it may be polycystic. Bronchography usually demonstrates failure of filling in the area even when fluid and air levels are present. Angiocardiography appears to be the best method (method of Robb and Steinberg, *American Journal of Roentgenology* 41:1-17, 1939, recommended). In children the rapid circulation time may necessitate the use of the aortogram. The importance of recognition is in the surgical approach, for fatalities have occurred because of the failure to recognize the origin of the artery to the lesion.

Pediatrics, Springfield, Ill.
Abstracted by W. W. Cleveland, M.D.

21, No. 6 (June) 1958

* Nephrectomy in Juvenile Hypertension Associated with Renal Disease: Report of 15 Cases. Herbert C. Welch, Lloyd E. Harris, and James H. DeWeerd.—p. 941.

22, No. 1 (July) 1958

* Hypertonic Dehydration (Hypernatremia): The Role of Feedings High in Solutes. Eleanor Colle, Elia Ayoub, and Richard Raile.—p. 5.

22, No. 2 (Aug.) 1958

* Insulin-Producing Capacity of the Pancreas of Children with Diabetes Mellitus. R. Klein, J. Marks, and I. A. Mirsky.—p. 289.

Nephrectomy in Juvenile Hypertension Associated with Renal Disease: Report of Fifteen Cases.—This study reports the experience of the Mayo Clinic over the past 20 years with the performance of nephrectomy for the treatment of hypertension considered to be secondary to renal ischemia. Of a total of 15 cases, 11 were felt to have unilateral renal disease, while in 4 the disease was thought to be bilateral.

Results of nephrectomy in amelioration of hypertension are reported according to defined criteria as good, equivocal, and poor, and further reported as to the initial and late response. Of 11 patients with unilateral renal involvement, 8 patients showed a good and 3 an equivocal response initially; 9 of these patients could be treated, and of these 6 showed a good late response, 2 an equivocal response, and 1 a poor response after follow-up periods of from 1½ to 11 years.

In four patients with bilateral renal disease, nephrectomy was performed in an effort to remove the most severely involved kidney. All four of these patients showed a poor response, both initially and in later follow-up.

The significance of these results is discussed as are the related symptomatology and the investigative procedures indicated in the study of a child with unexplained hypertension.

Comments: This article reports a further experience confirming the fact that a significant number of children manifesting hypertension may have a curable condition with unilateral renal ischemia. In by no means all of these patients is the renal involvement evident by the usual tests for renal status; indeed, in some cases, as pointed out by the authors, neither excretory nor retrograde urography may reveal the lesion, and it may be demonstrated only

by aortography. These authors advocate the translumbar approach, although in other centers retrograde catherization of a femoral artery is preferred. At any rate, it is important to emphasize the necessity for carefully studying any child manifesting prolonged hypertension without an apparent explanation.

Hypertonic Dehydration (Hypernatremia): The Role of Feedings High in Solutes.—The authors report an experience with an epidemic of gastroenteritis in infants and young children involving 32 patients admitted to the hospital for treatment. Of these, 25 had sufficient laboratory study to be classified as to the presence of hypernatremia.

According to the criteria of Na>150 or Cl>125, 17 infants were found to be hypernatremic; of these 4 died, while there were no deaths in children not manifesting hypernatremia. No specific infectious agent was demonstrated to be responsible for the epidemic.

The studies reported here are concerned with factors which may have contributed to the hypernatremia occuring in an unusually high incidence. Of particular significance was an analysis of the types of oral feedings given to three infants in the phase of their illness prior to hospitalization. There was great variety in these feeding programs, involving various milk formulae and oral electrolyte solutions. The composition of feedings in many cases of hypernatremia was such as to suggest that the solute to water ratio was too high to appropriately supply the demands of the infant losing fluid by diarrhea and other routes, thereby contributing to the resulting hypernatremia. The implications of these findings are discussed along with recommendations as to the avoidance of this complication by supplying a sufficient amount of solute-free water to compensate for losses.

Comments: This report was considered of sufficient importance to have included in the same issue of the Journal an editorial comment on the subject by Dr. Laurence Finberg. He points out that the increasing incidence of hypernatremia in infants with gastroenteritis is apparently real and that it may be due in part to faulty practices in management. Dr. Finberg suggests that careful directions must be given to the mother both as regards the correct dilutions of oral electrolyte solutions as well as limitation of the total amount of such solutions to be administered in a given period. Both the original article and the editorial comments point our principles of management which should be carefully considered by anyone undertaking the treatment of patients with diarrhea.

Insulin-Producing Capacity of the Pancreas of Children with Diabetes Mellitus.—The cause of diabetes mellitus in the child suggests that early in the course of the disorder the pancreas retains some of its capacity to produce insulin and that this capacity diminishes as the disease progresses.

In an attempt to measure this function, the authors measured the response of both normal and diabetic children of various stages of their disease to the administration of tolbutamide and indole-3-acetic acid. Both of these agents appear to be dependent upon the presence of insulin for the reduction of blood sugar; indole-3-acetic acid may exert its effect by the inhibition of insulinase. In an analysis of the data obtained, it was found that the hypoglycemic effect of both these agents in diabetic children could be correlated to a high degree with the duration of their disease.

During the first two years there was a very definite hypoglycemic response, which was not evident when the disease had been present for longer periods of time. It was concluded, then, that these data support the concept that the pancreas retains its ability to produce insulin early in the course of the disease, but eventually becomes completely exhausted as regards its capacity to produce insulin.

Comments: This study has considerable theoretical interest as regards the disturbed physiology of diabetes mellitius as well as some obvious implications regarding the use of tolbutamide either as a diagnostic or therapeutic tool in young diabetes. Many authorities would, however, not accept entirely the premise that indole-3-acetic acid exerts its influence by the inhibition of insulinase.

Radiology

Abstracted by William E. Anspach, M.D.

71, No. 3 (Sept.) 1958

* Hydrocarbon Pneumonitis. Frederick J. Bonte and Jack Reynolds.—p. 391.

Hydrocarbon Pneumonitis.—A study of 60 patients who had radiographic examinations following the ingestion of hydrocarbons showed x-ray signs consisting of pulmonary infiltra-

tions. In 48 cases kerosene was the poisoning agent. Twelve other cases were accounted for by hydrocarbon products commonly found in the home, such as gasoline, paint, turpentine, lighter fluid, several brands of furniture polish, cleaning fluid, and insecticides. Usually the amount of toxic agent ingested was unknown and could not be estimated with any degree of certainty. There was a definite correlation between the amount ingested and the severity of the symptoms, as well as the amount of visible infiltrate on x-ray films.

A history of spontaneous or induced vomiting was obtained in one-third of the cases but there was no real correlation between a history of vomiting and the extent of the disease. Obviously hydrocarbon pneumonitis was not dependent upon the mechanism of vomiting according to the histories obtained in this group.

Physical examinations revealed signs consistent with the presence of pulmonary consolidation in but 40% of the cases, whereas radiographically demonstrable infiltrates were present in almost all. Gavage did not appear to affect the extent of the disease as observed on roentgenograms, nor did it in any way lessen the length of hospital stay.

In this group four had no evidence of an abnormal shadow on chest films. Twenty-two had more than 10% and less than 20% of the lung area involved. Three had more than 30% of the lung area involved. The quality of the infiltrates ranged from soft flocculent to homogeneous. The commonest distribution was bilateral basal (38 cases). The least common was at the right base (8 cases).

Characteristically, resolution of the radiographically recognizable infiltrate lagged well behind clinical improvement and the period of resolution varied considerably, sometimes persisting as long as 12 days. Occasionally an initially small infiltrate became more extensive and pleural effusion developed. When this occurred it was the opinion of the pediatricians that a secondary infection had occurred. There was no fatality in this group. The average hospital stay was four days. The appearance of infiltrates on films was often rapid, in one instance a maximum of 12 minutes after the injection of the toxic material.

By cinefluorographic exposure on dogs following the injection of 15 cc. of kerosene into a main bronchus, the authors were able to demonstrate the appearance of the infiltrate in from 15 to 20 minutes. This grew steadily in size until death occurred at approximately three hours.

Zeitschrift für Kinderheilkunde, Berlin

Abstracted by Gunnar B. Stickler, M.D.

81, No. 2 (June) 1958

Time Relationships in the ECG of Healthy Infants During the First 100 Days of Life. W. Fuhrmann.—p. 131.
Cell Respiration and Virus Enzyme: Second Report. H. Stickl and H. Böcker.—p. 141.
Studies Regarding the Etiology of Plasma-Cell Pneumonia in Infants. L. Moser.—p. 152.
Extent and Interpretation of Aminoaciduria in Infants with Acute Nutritional Disturbances. M. Kleinbaum.—p. 158.
Congenital Unilateral Lesion of the Spinal Vasomotor System with Trophic Disturbances. P. Krepler.—p. 171.
Is the Causative Organism of the Interstitial Plasma-Cell Pneumonia a Virus Belonging to the Group of ADC Viruses? L. Vivell and G. Lips.—p. 181.
Therapy and Prophylaxis of Neonatal Tetanus. J. Paul.—p. 183.
* Pyelonephritis Due to Staphylococcus: The Most Frequent Complication of Pyodermias in Infancy. W. Rupp.—p. 200.
Studies Regarding the Interpretation of Efficiency Ranges in the Maturing Child. M. D. Kirchhoff, H. Reindell, and Ch. Hauswaldt.—p. 211.
Hormones of the Adrenal Cortex and Rickets. F. Thoenes and P. Schröter.—p. 239.

81, No. 3 (July) 1958

* The Treatment of Prematures in Warm or Cold Environment. H. Wagner.—p. 261.
The Plus and Minus Variation of Weight Gain During the First Trimenon. Ch. Scholz and E. Scholz.—p. 271.
Crouzon's Syndrome Combined with Changes of Arthromyogryposis and Partial Giantism. R. Beckmann and B. Jakobfeuerborn.—p. 293.
* The Prognosis of Infantile Progressive Spinal Muscular Atrophy of the Werdnig-Hoffmann and Oppenheim Types. U. Zeidler.—p. 315.
The Action and Side-Effects of Vitamin K Preparations in the Newborn Period. H. Haupt and H. Krebs.—p. 330.
Lipocalcinogranulomatosis (Teutschlaender's Disease). S. Apak.—p. 348.
The Intestinal Flora of Prematures in a Hospital Environment During Feeding of Fresh and Boiled Breast Milk. K. Hoffmann and H. U. Sauerbrei.—p. 367.
Acute Hemolytic Anemia with Methemoglobinemia and Methemalbuminemia in a Newborn, Probably Due to Naphthalin. K. Betke and H. Schall.—p. 379.

81, No. 4 (Sept.) 1958

Actions of the Influenza Virus: Fever and Inflammation. H. Stickl and H. Böcker.—p. 389.
The Importance of the Nitrate Content of Vegetables in Infant Nutrition. W. Kübler.—p. 405.
Acute Fetal Intoxication Due to Potassium Dichromate. J. Kuhle, E. Scheibe, and Bernt.—p. 417.
The Coagulation in Leukemia. W. Künzer, J. Ströder, and I. Hoffmann.—p. 431.
Studies of Fat Metabolism in Early Infancy. K. Schreier.—p. 442.
Foam Appearance [of Pneumoencephalograms] and Fatty Acids of Liquor. K. H. Auer.—p. 448.
Electrophoresis of Liquor in Neurologic Diseases of Children. E. Machetanz and D. Habeck.—p. 454.
* Transaminase and Glucolytic Enzymes in the Serum of Newborns, Infants, and Children. U. Stave.—p. 472.
Aminoaciduria in Rickets. J. Hanquet and H. Ewerbeck.—p. 481.
Spirographic Examinations for the Determination of Pulmonary Function in Children and Adolescents. H. D. Renovanz.—p. 494.

Pyelonephritis Due to Staphylococcus, the Most Frequent Complication of Pyodermas in Infancy.—The author stresses the relative frequency of hematogenous pyelonephritis in infants affected with staphylococcal pyodermas. He cites evidence from the literature that renal infection is frequent in staphylococcal sepsis in experimental animals. He has studied 50 infants with staphylococcal skin infection: 10 had the infection for more than four weeks; 23 had it for one to two weeks. Catheterized urine specimens obtained after careful cleansing were used for bacterial counts according to the method of Sanford, and the leukocyte count in the urine was determined also. A bacterial count of more than 10,000 per cubic centimeter, in addition to a leukocyte count of more than 10 per cubic millimeter and a decreased excretion of phenol red, was thought to be indicative of pyelonephritis. By these criteria, 31 of the patients were found to have pyelonephritis and four others had bacteriuria without apparent predisposing cause. Two-thirds of the patients had a reduced phenol red excretion.

Two-thirds of the infants were dismissed with bacteriuria of less than 10,000 per cubic centimeter. Of 14 patients reexamined after four weeks to eight months, 8 were found to have pathologic bacterial counts. [The follow-up of affected patients was inadequate]. The author thinks this type of pyelonephritis may be one reason for scars in human kidneys in 15% of all necropsies.

The Treatment of Prematures in Warm or Cold Environment.—The title of this paper is misleading. The author compares two groups of prematures, one having been kept in bassinets with three additional hot water bottles, the other in "preheated bassinets, protected from excessive heat loss." The first group included 52 infants observed in the years 1953 to 1954, the second group 38 infants observed during 1956 and 1957.

The groups were not matched in regard to sex and birth weight. The author observed that the body temperatures of the infants in both groups were similar after three weeks and that the latter group had a daily weight increase 20% higher than the first group.

This reviewer notes that the study was not well controlled in regard to environmental temperatures, that the groups were not observed simultaneously, and that the groups were not known to be similar in regard to birth weights. The author's conclusions may well be true, but are not proved by this study.

The Prognosis of Infantile Progressive Spinal Muscular Atrophy of the Werdnig-Hoffmann and Oppenheim Types.—The author attempted a follow-up study on 67 patients diagnosed as having amyotonia congenita (Oppenheim) or progressive muscular atrophy (Werdnig-Hoffmann) during the past 50 years in the Universitäts-Kinderklinik München. He was able to get information about 51 patients. In seven instances it was necessary to change the original diagnosis. One patient had reached the age of 29 years; 34 had died. The author reemphasizes the inability to differentiate the syndromes described by Oppenheim and by Werdnig and Hoffmann, but considers the former a congenital and severer form of the same disease process. On the basis of case descriptions of the surviving patients he outlines the possible course of the disease.

Transaminase and Glucolytic Enzymes in the Serum of Newborns, Infants, and Children.—The author determined values of serum GOT, serum GPT, serum aldolase, and serum lactic acid dehydrogenase in normal infants and children.

As in all reports published by Stave, the number of specimens examined was adequate and the methods are carefully described. His results are plotted in the form of scatter diagrams. The mean values and standard deviations are calculated for the various age groups.

Higher values for all enzymes were found in the newborn period, with relatively little change after the fourth week of life as adult values were approached.

Abstracts from the Soviet Literature

A selection of abstracts drawn from the current issue of Abstracts of Soviet Medicine, *a quarterly journal published by the Excerpta Medica Foundation (New York Academy of Medicine Building, 2 E. 103d St., New York 29), with the aid of a grant from the U. S. Public Health Service.*

Growth, Development

Physical development of children in Moscow in their first year, according to investigations in 1956 (Fizicheskoe razvitie detei pervogo goda zhizni v Moskve po dannym obsledovaniya 1956 g.). KOGAN R. Institute of Pediatrics, USSR Academy of Medical Sciences, Moscow *Pediatriya* 1957, 8 (67-75).

Anthropometric measurements (height, weight, circumference of head and chest) of 3,500 children in different parts of Moscow were taken in 1956. Comparison of the results of this investigation with the data of 1935 indicates that the weight of 6-month-old children increased by 500 g. and of those 12 months old by 925 g.; height at 6 months increased by 1.5 cm., and at 12 months by 2 cm.; the circumference of the chest increased by 2 cm. and of the head by 1 cm. These data indicate a high level of physical development of the children. There are now new laws applicable to the rate of increase of weight of children at this particular age group. Thus, the weight is doubled not at 6 months but at 4½ months and trebled at 12 months. The average circumference of the head and chest increases relatively fastest between the 3rd and 4th months and not between the 5th and 6th months as previously observed. Maximum increase in weight and height occurs in the 2nd month. Kvasnaya — Leningrad

Newborn Period, Prematurity, Embryopathy

Serum proteins of newborn babies and their mothers (Belki syvorotki krovi novorozhdennykh detei i ikh materei). LAVROVA V. I. *Vopr. Okhr. Mater. i Dets.* 1957, 2 (27-35).

Total serum protein and its fractions (albumin, α-, β-, γ-globulins) were estimated in 100 full-term and 35 premature babies and their mothers. The total protein content was lower after labour at term than in non-pregnant women. Total proteins and the content of protein fractions in the serum of the full-term baby were not related to sex and weight. There was a direct relationship as regards total protein, albumin and γ-globulin concentrations in the sera of the full-term baby and of its mother. This observation is of practical importance: anything which influenced the concentration of maternal serum proteins would be reflected in that of the foetus. Total serum protein concentration of the foetus increased pari passu with intrauterine development. Total serum protein concentration was lower in women entering upon labour prematurely than at term. Total protein concentration and especially the concentration of albumin and γ-globulin in the serum is much lower in premature babies than in full-term infants. Administration of amino acids, protein hydrolysate or γ-globulins is therefore indicated in prematurity. Low concentration of serum proteins is one of the causes of poor resistance to infections shown by premature babies.

Blood, Hemopoietic System, Blood-Group Antagonism

Haemolytic anaemia in the newborn (O gemoliticheskoy anemii u novorozhdennykh detei). NAZARENKO M. T. *Zdravookhr. Kir.* 1956, 5 (26-30).

Eight newborn children with haemolytic anaemia were the subject of investigation. Jaundice usually appeared on the 3rd or 4th day of life; enlargement of liver and spleen and dyspnoea were observed. Two children died on the 1st and 5th day of illness. Treatment consisted of transfusion with Rh-negative blood in quantities of 5-8 ml. per kg. body weight, and administration of campolon, neohepar, vitamins C and B_1, glutamic acid, vikasol (vit. K), iron and glucose.

Gastrointestinal System

Clinical features, early diagnosis and treatment of salmonellosis (mouse typhoid) in early childhood (Klinika, rannyaya diagnostika i lechenie salmonelleza (myshinogo tifa) v rannem detskom vozraste). GURVICH B. I., BLINDOVSKAYA R. A., GARANINA S. A. and KOLOBIKHINA S. A. Department of Clinical Pediatrics, Medical Institute, Gorky *Pediatriya* 1957, 4 (30-33) Tables 2.

In the past few years, salmonellosis, due to a Breslau type strain (S. typhimurium) has considerably increased among very young children. The incubation period varies from a few hours to 1-2 days. The severity of the disease depends upon the degree of infection and the child's power of resistance. The reservoir of infection of Salmonella of the Breslau type is rats which contaminate food with their excrements. Another possible source of infection is "carriers." Salmonella appears as an enteric infection attacking by preference the small intestine in the form of an enteritis. However, it has also been found to attack the large intestine with catarrh. Young children are most often affected, especially those suffering from marasmus or rickets, also bottle-fed babies and those partially bottle-fed in early infancy. The deciding factor in diagnosing a Salmonella infection are the positive findings of the analysis of the stools of the patient during the first two or three weeks of the illness. In the earlier stages of the disease, Salmonella may be detected in bacteriological analysis of the urine and blood of the patient. The clinical picture of the disease is varied; according to whichever feature is dominant, the following forms of the disease can be discerned: Pulmonary, digestive and colitis. Characteristic symptoms are: fluctuating temperature with some high swings, and pallor of skin, sometimes with pronounced cyanosis. At the onset of the disease toxaemia is found in 70% of the patients and is accompanied by vomiting and distension of the abdomen. The patients have 4 or 5 bowel movements a day, and the stools are loose, watery, greenish and sometimes admixed with blood. In 70% of the children the liver and spleen are enlarged. The blood shows a moderate leucocytosis, neutrophilia and a moderately accelerated ESR. Patho-anatomical findings include catarrhal, haemorrhagic and malignant enteritis, affecting the small intestine and also fatty degeneration of the liver, hyperplasia of the spleen and degenerative changes in the heart and liver. Treatment should be directed primarily towards combating toxaemia and auto-toxaemia by way of plenty fluids and saline administration followed by regular feeds with administration at the same time of synthomycin (chloramphenicol) and biomycin (chlortetracycline), blood transfusions and vitamins.

Urogenital System

Significance of acute tonsillitis in the aetiology of acute diffuse glomerulonephritis in children (Znachenie angin v etiologii ostrogo diffuznogo glomerulonefrita u detei). CHIRESHKIN D. G. Second Children's Municipal Clinical Hospital, Moscow *Pediatriya* 1957, 6 (49-52).

During the investigation of case histories of 119 children (aged from 1 yr. 6 months to 14 yr.) with diffuse glomerulonephritis, it was found out that foremost among the illnesses preceding the nephritis and having an aetiological relation to it was tonsillitis (39.5%) followed by catarrh of the upper respiratory passages (20%), and acute infections of childhood (17.6%), including scarlet fever (13.9%). Thus, at the present time scarlet fever has lost its leading importance in the aetiology of diffuse nephroses. Acute diffuse nephritis developed generally 2 weeks after the onset of an attack of tonsillitis. Prevention of tonsillitis is the best preventive measure against acute diffuse glomerulonephritis.

Skin, Teeth, Hair, Nails

Role of vitamin A and carotene in some skin diseases of infants in their first year of life (Vitamin A i karotin pri nekotorykh kozhnykh zabolevaniyakh u detei pervogo goda zhizni). ZVERKOVA F. A. *Vopr. Okhr. Mater. i Dets.* 1957, 2 (19-27).

Blood concentration of vitamin A and carotene of breast-fed infants suffering from various skin diseases and of their mothers was studied. A control group of healthy babies and their mothers was also investigated. It was found that: (1) Vitamin A and carotene contents of the blood of healthy infants under one year of age show seasonal variation and changes dependent on the type of feeding. (2) In the case of erythroderma desquamativum the blood level of those substances is greatly lowered. (3) This fall depends on both exogenic and endogenic factors (gastrointestinal disorders, disorders of liver function). (4) Vitamin A and carotene concentration in the blood and milk of mothers breastfeeding babies suffering from erythroderma desquamativum is low. Addition of those substances to the diet of the mothers constitutes an integral part of the treatment. (5) In dermatitis herpetiformis of the newborn the blood levels of vitamin A and carotene are low. This fall becomes even more accentuated in exfoliative dermatitis. (6) In cases of infantile eczema the amounts of circulating vitamin A and carotene are larger than normal as a result of interference with general metabolism. (7) Administration of vitamin A to infants suffering from eczema helps in restoration of normal metabolism. Administration of vitamin A during pregnancy, especially

in cases of toxaemia of pregnancy, is an important factor in prevention of skin disease in infants.

Cholesterol metabolism in exudative diatheses of children (Kholesterinovyi obmen u detei s ekssudativnymi kozhnymi yavleniyami). GERI E. I. *Sborn. Trud. Inst. Okhr. Mater. i Dets.* 1956, 7 (251-262).

A series of 50 children aged one month to four years and suffering from exudative diathesis were investigated. It was demonstrated that the dermal manifestations in these cases are closely related to abnormalities of metabolism, as shown by high peptide nitrogen and low cholesterol in the blood. The severity of the condition of the skin increases with blood peptide nitrogen rise and blood cholesterol fall. Adjustment of diet to the age and weight of the child and its prolonged supervision give good results.

Bones, Muscles, Joints

Treatment of congenital dislocation of the hip in the newborn and in early infancy (Lechenie vrozhdennogo vyvikha bedra u novorozhdennykh detei i u detei rannego detstva). GULYAEVA N. M. *Vopr. Travm. i Ortop.* 1956, 1 (97-100).

Dislocations and subluxations of the hip joint occupy an important place among the congenital malformations and diseases of the locomotor apparatus. Successful outcome depends on early diagnosis and correspondingly early treatment, which is only possible through cooperation of obstetrician, pediatrician and orthopaedic surgeon. The cardinal sign of congenital dislocation of the hip in the newborn is, according to Marks, the phenomenon of overriding. In infants up to 3 months it is manifested by the sign of telescoping accompanied by a characteristic click, according to Schneider. In the newborns, sometimes a slight looseness in the hip may be noted. Other symptoms, such as a pronounced rotation of the hip and asymmetry of skin folds are not characteristic. Early treatment within the first weeks of life, after the disappearance of muscular spasm, is relatively simple under hospital conditions, and gives good results. It consists of placing the child flat on the abdomen, then the legs are placed apart at an angle of 90°. An individual half bed plaster splint is applied allowing for maximal rotation, abduction and flexion (1st position of Lorenz). The treatment usually takes 3-4 months under constant X-ray control, which is of special importance during the first 3-4 days. The dislocation is considered to be reduced when the acetabulum forms a hemisphere and the ossification centre is situated centrally in the joint cavity. It is essential to instruct the child's mother how to nurse the child and how to take care of the plaster splint. Both anatomically and physiologically the result of treatment in the newborn is permanent.

Acute Infectious Diseases

Reduction of the morbidity and mortality rate due to pertussis (Osnovnye puti k snizheniyu zabolevaemosti i letalnosti ot koklyusha). DOBROKHOTOVA A. I. *Pediatriya* 1957, 1 (3-8).

Anti-epidemic measures, including early diagnosis, causal therapy and prophylaxis are the essential means of reducing the morbidity and mortality rates of pertussis. Considering that clinical diagnosis at the onset of the disease in the absence of typical symptoms is difficult, the author underlines the necessity for a careful epidemiological analysis of all cases of cough. Early treatment and correct regime can prevent a severe course. The first task in a complex therapy is to eliminate the irritation of the peripheral receptors; this can be achieved by the administration of antibiotics and specific sera or γ-globulin. Secondly, a regime is necessary which prevents the development of oxygen insufficiency and promotes a speedy restoration of the impaired functional balance. Streptomycin is most effective, especially if given early. A cyclic method of antibiotic treatment is convenient. Injection of specific sera and of γ-globulin is also effective in the early stages of the disease. A correct regime in the hospital is very important, and patients who have completed the antibiotic treatment should not be allowed to come into contact with new cases. Early treatment, correct regime and convalescence of the child in a sanatorium are essential measures in the campaign to reduce mortality due to pertussis.

Investigation of biological characteristics of haemolytic streptococci in superinfection and complications of scarlet fever (Izuchenie biologicheskikh svoistv gemoliticheskikh streptokokkov pri superinfektsii i oslozhneniyakh skarlatiny). PERVACHENKO S. V. *Pediatriya* 1957, 1 (15-22).

Fifty-four cases of scarlet fever in children were under observation. The first group consisted of cases with uncomplicated clinical course of scarlet fever. Haemolytic streptococci

isolated from them during convalescence with change of serological types were less toxigenic than original strains. Haemolytic streptococci isolated both at the beginning of the disease and during convalescence but without serological type change were equally toxigenic. In the second group were cases of relatively uncomplicated clinical course of scarlet fever but with subfebrile temperature following the acute stage of the disease. In these cases there was change of serological type of streptococcus. Higher toxigenic indexes were found in the subfebrile period. Cases with late complications of scarlet fever were in the third group. The change of serological type of the haemolytic streptococci coincided in time with the period of complications; the toxigenic qualities of haemolytic streptococci in the period of complications were considerably higher than those of the original strains. In the fourth group were cases with recurrent scarlet fever tonsillitis. The toxigenic action of the strains isolated in the period of secondary tonsillitis was considerably higher than that of the strains isolated at the beginning of the disease. In all these cases there was a change of serological type of haemolytic streptococci. Results of the investigation prove the role of toxigenic strains in the pathogenesis of scarlet fever complications. The author maintains that in reinfection with new serological types complications occur only when they are more toxigenic than the original strains. There was no correlation between the clinical course of scarlet fever and the toxigenicity of the strains.

Aerosol inhalation of penicillin as a method of prophylaxis of scarlet fever otitis (Aerozolnye ingalyatssi penitsillina kak metod profilaktiki otitov priskarlatine). UMANSKII Ya. P. and PRIKHODKO E. I. *Pediatriya* 1957, 1 (35-36).

The influence of aerosol inhalation of penicillin on throat flora was investigated. For pulverization of penicillin an apparatus was used, whereby pulverization was obtained by the use of compressed air under a pressure of 0.2-0.25 atmospheres. Inspiration through the mouth and expiration through the nose was used; duration of the procedure was 15 minutes. Inhalation was prescribed in the first days after admission, once in 6 days. 100 children were under observation. Only 17 developed a complication in the form of an allergic wave. In the control group (no inhalation used) complications were seen in 42% of cases, mostly catarrhal and purulent otitis (39%). The strongest concentration of penicillin was observed 3 hours after inhalation. When penicillin aerosol application is not possible, the authors recommend nasal instillations of penicillin solution 200,000 to 300,000 U. in 10 ml.

Rheumatic Diseases

Aetiology of rheumatic nephritis (K voprosu o patogeneze porazheniya pochek pri revmatizme). BENDERSKAYA S. M. *Pediatriya* 1957, 2 (23-28).

Experiments were carried out on 29 rabbits sensitized to (a) normal horse serum, (b) healthy human serum, (c) human serum after single injection of caffeine, (d) serum of patients suffering from rheumatic disease, with a subsequent precipitating injection of the same serum. Sensitization of rabbits with the sera produced in their kidneys allergic changes of various intensity. The most appreciable changes were found in kidneys of rabbits sensitized with serum of rheumatic patients, and in rabbits which were for a long time used in experiments. In these rabbits changes in kidneys closely resembled those found in children who had died of rheumatic disease. Administration of caffeine intensified the renal lesions. Changes in other organs (myocardium, liver, spleen) were of the same kind, which confirms their common allergic aetiology. Attention is drawn to an increase of arterial pressure at the time of the precipitating injections.

Miscellaneous

Patho-anatomical studies on infant mortality during 1949-1953 (Patologo-anatomicheskoe issledovanie detskoi smertnosti za 1949-1953). SHILEV P., DRAGIEV M., AGOPYAN K., SOLOV K. and MILENKOV KH. *Sovr. Med.* 1956, 8 (3-7).

In the course of 5 years 1,060 autopsies on children up to the age of 14 were performed at the University hospital in Plovdiv; 25.37% of these had died from respiratory disease, 22.83% from infectious diseases (diphtheria, pertussis complicated by bronchopneumonia, sepsis, measles, cerebrospinal meninigitis, dysentery etc.); 11.5% from tuberculosis; 9.6% from digestive disorders (enterocolitis, peritonitis, cirrhosis of the liver etc.); 1.22% from viral infections (hepatitis, poliomyelitis) 0.94% from avitaminosis and 6.21% from cardiovascular disorders and haemopoietic disturbances (endocarditis, congenital heart disease, rheumatic endocarditis, leukaemic lymphadenomatosis, myeloma, acute myelitis, haemorrhagic diathesis etc.).

News and Comment

ANNOUNCEMENTS

Institute on Medical Teaching.—The Second Summer Institute on Medical Teaching jointly sponsored by the University of Buffalo and the Association of American Medical Colleges will be held in Buffalo, June 9-18, 1959. The Institute will provide an opportunity for medical instructors to join specialists in Education in an examination of teaching and learning in medical schools. Included in the presentations, demonstrations, and discussions led by University of Buffalo faculty from the Schools of Medicine, Education, and Arts and Science will be such topics as the nature of learning; the nature of medical students and medical faculties; the philosophical background for higher education in the United States; the use of the lecture and laboratory, ward exercise and clinical conference, as well as less familiar methods of instruction; the use of tests and other appraisal devices for measuring student performance in a Medical School. Opportunity for consultation on individual instructional problems will also be provided.

Attendance at the Institute will be limited. Interested members of Medical School faculties in the United States and Canada may apply for registration or further information by writing to Dr. George E. Miller, Associate Professor of Medicine, University of Buffalo School of Medicine, Buffalo 14.

Speech Clinic and Hearing Laboratory, Marquette University.—The summer program in Speech Correction at Marquette University will offer three workshops in speech correction for two to six credits each. The Beginning, Advanced, and Graduate Workshops will be held from June 22 through July 31, 1959. Students will be able to elect credits in various course areas within the scope of the above. Clinical work with patients is an essential part of each workshop.

A two-week Institute on Speech Correction For The Classroom Teacher will be held from June 29 through July 10 for two credits. Graduate and undergraduate credit may be earned. The Institute will consist of demonstrations, closed circuit television instruction, and clinical work with articulation cases.

Sessions will be held from 1-4 p.m., Monday through Friday.

Further information on the workshops and the Institute may be obtained by writing to the Director of the Speech Clinic, School of Speech, Marquette University, 625 N. 15th St., Milwaukee 3.

Alan Moncrieff to Speak in Baton Rouge.—The Baton Rouge Pediatric Society wishes to announce its June 16 quarterly meeting, which will consist of a program by Dr. Alan Moncrieff, Chief of Staff, The Hospital for Sick Children, Great Armond Street, London, England. The subject will be "Biochemistry and Mental Defects."

Anyone desiring further information, please contact Francis M. Harris, Jr., M.D., Secretary-Treasurer, Baton Rouge Pediatric Society, 1401 N. Foster Drive, Baton Rouge, La.

Books

BOOKS RECEIVED

Allergy in Pediatric Practice. By Sherman and Kessler. Price, $9.25. Pp. 296. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis, 1957.

Autonomic Imbalance and the Hypothalamus. By Ernst Gellhorn. Price, $8.50. Pp. 300. University of Minnesota Press, Minneapolis 14, 1957.

Baby and Child Care. By L. Emmett Holt Jr. Price, $4.95. Pp. 288. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

* **Chemical Anthropology: A New Approach to Growth in Children.** By Icie G. Macy and Harriet J. Kelly. Price, $3.75. Pp. 149. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1957.

Current Therapy 1958. Edited by Howard F. Conn. Price, $12. Pp. 827. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

Diabetes as a Way of Life. By T. S. Danowski. Price, $3.50. Pp. 177. Coward-McCann, Inc., 210 Madison Ave., New York 16, 1958.

Diseases of the External Ear. By Ben H. Senturia. Price, $8.50. Pp. 211. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

* **Einführung in die Kinderheilkunde.** By E. Glanzmann. Price, $17.85. Pp. 1068. Springer-Verlag, Mölkerbastei 5, Wien I, 1958.

* **L'Enfant Inadapte.** By L. Michaux and D. J. Duche. Price, 3,600 fr. Pp. 316. Gaston Doin & Cie, 8 place de l'Odéon, Paris 6e, 1957.

* **Enuresis: A Clinical and Genetic Study.** By Bertil Hallgren. Price, not given. Pp. 159. Ejnar Munksgaards Forlag, Nørregade 6, Copenhagen, 1957.

* **Hemophilia and Hemophilioid Diseases.** Edited by Kenneth M. Brinkhous. Price, $7.50. Pp. 265. University of North Carolina Press, Chapel Hill, 1957.

Heredo-Retinopathia Congenitalis: A Genetical-Statistical Study. By Carl H. Alstrom. Price, not given. Pp. 178, Berlingska Boktryckeriet, Lund, Sweden, 1957.

The Incurable Wound. By Berton Roueche. Price, $3.50. Pp. 177. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

The Infantile Cerebral Palsies. By Collis, Collis, Dunham, Hilliard, and Lawson. Price, $3. Pp. 100. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

Laboratory Applications in Clinical Pediatrics. By Irving J. Wolman. Price, $15. Pp. 1019. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

* **Les Malformations congenitales du poumon.** By Breton and Dubois. Price, 2,200 fr. Pp. 140. Gaston Doin & Cie, 8 place de l'Odéon, Paris 6e, 1957.

Modern Perinatal Care. By Leslie V. Dill. Price, $6.50. Pp. 309. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1957.

* **Nierenkrankheiten: Physiologie, Pathophysiologie, Klinik und Therapie.** By Hans Saare. Price, $14.05. Pp. 540. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1957.

Oligophrenia in Combination with Congenital Ichthyosis and Spastic Disorders: A Clinical and Genetic Study. By Sjögren & Larsson. Price, not given. Pp. 109. Ejnar Munksgaards, Forlag, Nørregade 6, Copenhagen, 1957.

* Review has been published or is being prepared.

* **Die Physiologie des Lymphozytenwechsels und seine Beeinflussbarkeit durch Hormone des Hypophysen-Adrenalsystem.** By H. G. Hansen. Price, $4.40. Pp. 164. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

Practical Allergy. By M. Coleman Harris and Norman Shure. Price, $7.50. Pp. 471. F. A. Davis Company, Philadelphia 3, 1957.

* **Les régimes du nourrisson bien-portant ou malade.** By P. Delthil. 3,350 fr. Pp. 346. Gaston Doin & Cie, place de l'Odéon, Paris 6e, 1957.

Roentgen Diagnosis of Abdominal Tumors in Childhood. By Nice, Margulis and Rigler. Price, $4.00. Pp. 75. Charles C Thomas, Publisher, 301-327 Lawrence Ave., Springfield, Ill., 1957.

* **Toxoplasmose bei Mensch und Tier.** By O. Thalhammer. Price, $13.75. Pp. 307. Wilhelm Maudrich, Spitalgasse 1b, Wien IX, 1957.

Tracheotomy: A Clinical and Experimental Study. By T. G. Nelson. Price, $3.75. Pp. 111. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Psychopathology of Communication. Edited by Paul Henry Hoch and Joseph Zubin. Price, $6.75. Pp. 305. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1958.

Annual Review of Medicine: Volume 9. Edited by David A. Rystand and William Creger. Price, $7.00. Pp. 530. Annual Reviews, Inc., Grant Ave., Palo Alto, Calif., 1958.

Anomalies of Infants and Children. By Mayer and Swanker. Price, $12. Pp. 454. McGraw-Hill Book Company, Inc., 33 W. 42d St., New York 36, 1958.

Care of the Premature Infant. By Lundeen and Kunstadter. Price, $8.00. Pp. 367. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1958.

Clinical Enzymology. By G. J. Martin. Price, $6. Pp. 241. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

* **Hermaphroditism, Genital Anomalies and Related Endocrine Disorders.** By Howard W. Scott Jr. and William Wallace. Price, $16. Pp. 456. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Manual of Pediatric Physical Diagnosis. By Lewis A. Barness. Price, $4.00. Pp. 195, The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

Modern Prescription Drugs: Their Impact on the Family Budget. Price, not given. Pp. 43. Citizens' Committee for Children of New York City, 1958.

New Frontiers in Child Guidance. By A. H. Esman, Price, $4.00. Pp. 218. International Universities Press, 227 W. 13th St., New York 11, 1958.

Outline of Orthopaedics. Second Edition. By J. C. Adams. Price, $8.00. Pp. 428. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Practical Cardiology. By A. S. Hyman. Price, $7.00. Pp. 302. McGraw-Hill Book Company, Inc., 33 W. 42d St., New York 36, 1958.

Toys—The Tools of Children. By June Frantzen. Price, $1.00. Pp. 17. National Society for Crippled Children and Adults, Chicago, 1958.

Treatment of Acute Poisoning. By Bensley and Jordan. Price, $4.00. Pp. 212. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Wesen und Bedeutung der Enchondralen Dyostosen. By Hans Mau. Price, $6.40. Pp. 219. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

Pediatric Gynecology. By G. C. Schauffler. Price, $9.00. Pp. 349. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

Cerebral Palsy in Childhood. By Grace E. Woods. Price, $6.50. Pp. 158. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Modern Trends in Pediatrics. By Holzel and Tizard. Price, $14.00. Pp. 385. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1958.

Rehabilitation of the Cardiovascular Patient. By White, Rusk, Lee, and Williams. Price, $7.00. Pp. 176. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

Aktuelle Probleme der Kindertuberkulose. By H. Wissler. Price, $3.05. Pp. 71. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

Anaesthesia for Nurses. By Eric Godwin. Price, $2.50. Pp. 98. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Antisera Toxoids, Vaccines and Tuberculins. By H. J. Parish. Price, $7.00. Pp. 256. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Art Therapy in a Children's Community. By Edith Kramer. Price, $6.75. Pp. 238. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Child Care and Training. Eighth Edition. By Faegre, Anderson, and Harris. Price, $3.00. Pp. 300. University of Minnesota Press, Minneapolis 14, 1958.

Chirurgie préventive de la tuberculose ostéo-articulaire. By R. Kaufmann. Price (paper), 2,000 fr. Pp. 174. Gaston Doin & Cie, 8 place de l'Odéon, Paris 6e, 1958.

Cleft Palate and Speech. Fourth Edition. By Muriel E. Morley. Price, $6.50. Pp. 292. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

* **The Management of Childhood Asthma.** By Frederic Speer. Price, $4.75. Pp. 116. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Memories and Reveries. By Frederick E. Jackson. Price, $3.00. Pp. 153. The Exposition Press, Inc., 386 Fourth Ave., New York 16, 1958.

New Frontiers in Child Guidance. Edited by Aaron H. Esman. Price, $4.00. Pp. 218. International Universities Press, Inc., 227 W. 13th St., New York 11, 1958.

No More Tonsils! Revised Edition. By Ellen Paullin. Price, $2.00. Beacon Press, Inc., 25 Beacon St., Boston 8, 1958.

Orthopedic Diseases. By Aegerter and Kilpatrick. Price, $12.50. Pp. 602. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

Practical Pediatrics. By R. C. Eley and B. Kramer. Price, $7.00. Pp. 309. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

The Practice of Infectious Diseases By Louis Weinstein. Price, $8.50. Pp. 501. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

Principal Infectious Disease of Childhood. By Nelles Silverthorne. Price, $3.50. Pp. 102. University of Toronto Press, Toronto 5, Canada.

Les sinusites de l'enfance. By J. Terracol and Y. Guerrier. Price, 1,400 fr. Pp. 166. Masson & Cie, 120 boulevard Saint-Germain, Paris 6e, 1958.

Surgery in Infancy and Childhood. By M. White and W. M. Dennison. Price, $9.50. Pp. 444. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Traumatologie infantile. By Chigot and Esteve. Price, 5,000 fr. Pp. 358. Expansion scientifique française, 174 boulevard Saint-Germain, Paris 6e, 1958.

Non-Venereal Syphilis. By Ellis H. Hudson. Price, $7.00. Pp. 204. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Modern Problems in Pediatrics (in German, French, and English). By Hottinger, Hauser, and Berger. Price, 96 Sfr. Pp. 592. S. Karger A. G., Arnold Böcklinstrasse 25, Basel (American agent—Mr. Albert J Phiebig, P. O. B. 352, White Plains, N. Y.), 1958.

Nervöse Verhaltensstörungen beim Schulkind. By von Harnack. Price, $2.35. Pp. 92. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

L'Hydrocéphalie du nourrisson. By M.-R Klein. Price, 1,600 fr. Pp. 136. Masson & Cie, 120 boulevard Saint-Germain, Paris 6°, 1958.

Affections non congénitales de l'anus et du rectum chez l'enfant. By Jean Duhamel. Price, 3,600 fr. Pp. 264. Masson & Cie, 120 boulevard Saint-Germain, Paris 6°, 1958.

Pesudarthrose congénitale du tibia. By Guilleminet and Richard. Price, 1,800 fr. Pp. 98. Masson & Cie, 120 boulevard Saint-Germain, Paris 6°, 1958.

Care of the Premature Infant. By Lundeen and Kunstadter, Price, $8.00. Pp. 367. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1958.

Correlative Neuroanatomy and Functional Neurology. Eighth Edition. By Joseph G. Chusid and Joseph J. McDonald. Price, $4.50. Pp. 344. Lange Medical Publications, Box 1215, Los Altos, Calif., 1956.

Handbuch der Tuberkulose. Fifth Edition. Edited by J. Hein, H. Kleinschmidt, and E. Uehlinger, Volume I: Allgemeine Grundlagen, revised by H. Bloch et al. Price, $42.40. Pp. 832. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

The Medical Assistant. By Miriam Bredow. Price, $7.50. Pp. 430. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1958.

Paediatrics for Nurses. By Arthur G. Watkins. Price, $3.75. Pp. 200. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Physician's Handbook. Ninth Edition. Edited by Marcus A. Krupp and others. Price, $3.00. Pp. 500. Lange Medical Publications, Box 1215, Los Altos, Calif., 1956.

The Psychology of Medical Practice. By Marc H. Hollender, Price, $6.50. Pp. 276. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

Advances in Pediatrics. Volume X. By S. Z. Levine. Price, $9.00. Pp. 362. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1958.

Bibliography of Internal Medicine: Communicable Diseases. By A. L. Bloomfield. Price, $10. Pp. 560. University of Chicago Press, 58th St. and Ellis Ave., Chicago 37, 1958.

Cerebral Palsy. By J. Russ and H. Soboloff. Price, $4.00. Pp. 77. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Chronik der Kinderheilkunde. By Albrecht Peiper. Price, DM 51.20. Pp. 527. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

Discussions on Child Development. Edited by J. M. Tanner and B. Inhelder. Price, $5.00. Pp. 223. International Universities Press, Inc., 227 W. 13th St., New York 16, 1958.

L'enfant physiquement handicapé. By Clément Launay and D. J. Duché. Price, 2,600 fr. Pp. 195. Gaston Doin & Cie, 8 place de l'Odéon, Paris 6°, 1958.

Epilepsy Handbook. By F. A. Gibbs and F. W. Stamps. Price, $4.75. Pp. 101. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

Essentials of Pediatrics. Sixth Edition. By Philip C. Jeans, F. Howell Wright, and Florence G. Blake. Price, $6.00. Pp. 714. J. B. Lippincott Company, 231 S. Sixth St., Philadelphia 5, 1958.

Fortschritte der Kiefer- und Gesichts-Chirurgie. Edited by Karl Schuchardt. Price, $28.55. Pp. 441. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.
Corporation, 381 Fourth Ave., New York 16), 1958.

Human Blood in New York City. Pp. 147. New York Academy of Medicine, 1958.

* **Infectious Diseases of Children.** By Saul Krugman and Robert Ward. Price, $10 Pp. 340. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

Kinderärztliche Notfallfibel. Fourth Edition. By B. de Rubber. Price, $4.45. Pp. 205. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

Krankheiten der Neugeborenen. By A. Peiper. Price, DM 19.40. Pp. 131. VEB Georg Thieme, Hainstr. 17/19 Aufg. C, Leipzig C. 1, 1958.

Pediatric Surgery. By O. Swenson. Price, $20. Pp. 750. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1958.

Physical and Behavioral Growth: Report of the 26th Ross Pediatric Research Conference. Edited by J. Philip Ambuel. Pp. 101. Ross Laboratories, Columbus, Ohio, 1958.

Proceedings of the Ninth Annual Conference on the Nephrotic Syndrome. Edited by J. Metcoff. Pp. 248. National Nephrosis Foundation, 43 E. 35th St., New York, 1958.

Uber die Erblichkeit des Normalen Elektroenzephalogramms. By F. Vogel. Pp. 92. Georg Thieme Verlag, Stuttgart (American agent—Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16), 1958.

BOOK REVIEWS

Neuropathology. By J. G. Greenfield, W. Blackworth, W. H. McMenemey, A. Meyer, and R. M. Norman. Price, £5 5s. Pp. 640. Edward Arnold, Ltd., 41 Maddox St., London W1, 1958.

This competent and authoritative text on the pathology of central nervous system diseases represents the last major professional contribution of Dr. J. G. Greenfield, whose untimely death occurred shortly after the first edition became available.

In the initial chapters, the normally encountered histologic structures are carefully described. The spectrum of fundamental changes exhibited by ganglion cells under the influence of numerous agencies is also elaborated. In conjunction with this chapter, there is a lucid description of the various forms of particulate intracellular structures (inclusion bodies) characteristic of the central nervous system. Neuroglial embryology, morphology, and response to disease processes are meticulously assessed.

In the succeeding 12 chapters, various major categories of nervous system diseases are reviewed. (The problem of neural neoplasia is left in abeyance for a subsequent volume.) The first of these segments explores vascular abnormalities (insufficiency, hemorrhage, specific vascular disturbances, and aneurysms). The chapter concerning infectious processes within the nervous system represents an adequate survey and contains an unusually lengthy description of the forms and varieties of neurosyphilis. A thorough exploration of the structural changes consequent to intoxication and metabolic disorders is included, along with a clear discussion concerning the problem of selective vulnerability within the nervous system. The changes related to alcoholic intoxication are surprisingly brief, perhaps reflecting the comparative rarity of this problem in England. Nervous system malformations are logically considered in close association with the pathology of birth injury and intrinsic neural diseases of early life. This chapter is profusely illustrated, but irregularly documented. Central nervous system trauma is but briefly explored. Very few of the speculative excursions characteristic of other neuropathology texts are found, and only the incontrovertible structural changes are offered. Demyelinating diseases and abiotrophic disorders are presented, preceding the changes within the nervous system incident to aging. These descriptions are accompanied by segments devoted to the systematized dementias and dyskinesias. The final chapters are concerned with diseases of the peripheral nervous system and disorders of neighboring structures (viz., cranium and vertebra).

While some space is devoted to diseases of obscure substrate (e. g., schizophrenia), the vast majority of the text is consigned to a rational and conservative analysis of the neurocellular components in intracranial disorders. Corollary investigative findings generally precede each pertinent discussion. The text is clearly apportioned and well indexed. The photography and typography are technically superior. This work probably represents the most thorough reference on nervous system pathology available in the English language to date.

S. M. Aronson, M.D.

Care of the Premature Infant. By Evelyn C. Lundeen, R.N., and Ralph H. Kunstadter, M.D., F.A.C.P., F.A.A.P. Price, $8.00. Pp. 367, with 88 illustrations. J. B. Lippincott Company, 227-231 S. Sixth St., Philadelphia 5, 1958.

This book, according to the author, Miss Lundeen, was written in response to the many requests received by her from nurses for methods and techniques used in the Premature Infant Section at the Michael Reese Hospital. The text goes well beyond covering nursing methods and techniques and attempts to incorporate the medical aspects of prematurity, including etiology, physiologic development, feeding, therapy, including a chapter on antibiotics, as well as pathologic conditions. A chapter is devoted to later physical and mental development. Portions of the book as stated appeared formerly under the title "The Premature Infant" by Julius H. Hess, M.D., and Evelyn C. Lundeen, R.N., in 1941 and 1949.

There is much of a practical nature in the volume, and it is obviously written with a spirit of dedication and keen concern for the welfare of the premature. Breast-milk feeding is greatly stressed in its importance. The authors state: "We believe that breast milk is the ideal food for the premature and the immature infant." This belief has not been universally shared. At the present time it is more usual to find the premature centers feeding artificial formula (usually skimmed milk type). Comparison of survival by weight group of premature infants cared for at premature centers and at the Michael Reese Hospital does not seem to support the emphasis given. However, the last word may not have been said on this subject, and one must respect the strong convictions of the authors, who have had the benefit of many years of experience.

Miss Lundeen's stress on aseptic nursing techniques is more apropos today than ever with the realization that antibiotics given prophylactically will not ward off staphylococcal infection or replace rigid asepsis as a means of infection control.

In the chapter devoted to pathologic conditions and their management, resuscitation is discussed. Artificial respiration by means of the method of compressing and relaxing by means of the hand on the sides of the chest is mentioned. This method has been criticized by many as more harmful than helpful. Perhaps the authors should have given more emphasis to aspiration and keeping the airway open than to this method. True, they do state "careless handling . . . or too rapid performance of artificial respiration does more harm than good, and, therefore, must be avoided." Practical experience has shown apparently that when such a measure is resorted to zeal in its use (born of desperation perhaps) can lead to more harm than good. At present, too, the preponderance of opinion is that the Rockette is of limited value. Perhaps more time and experience are needed with this equipment before one can conclude with finality regarding its merits.

In the chapter on Therapeutic Procedures relating to oxygen therapy, this reviewer would have preferred to see much more emphasis given to controlled use of oxygen. Reliance cannot be placed on liter flow alone. Mention is made that oxygen percentage should be checked with an "oximeter" and charted in the nurse's notes. An oxygen analyzer of a reliable manufacture should be employed at least every six to eight hours as a check on the concentration of oxygen in the incubator.

It is commendable that a full-time nurse is employed for follow-up care of infants after discharge from the hospital and plans her first visit the day after discharge. This aspect of follow-up deserves more attention than is generally given.

Miss Lundeen and Dr. Kunstadter have paid fine tribute in dedicating this book to the memory of Dr. Hess, who pioneered in premature infant care.

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1. Perkins, J. L.: Kansas State M. J. (to be published).

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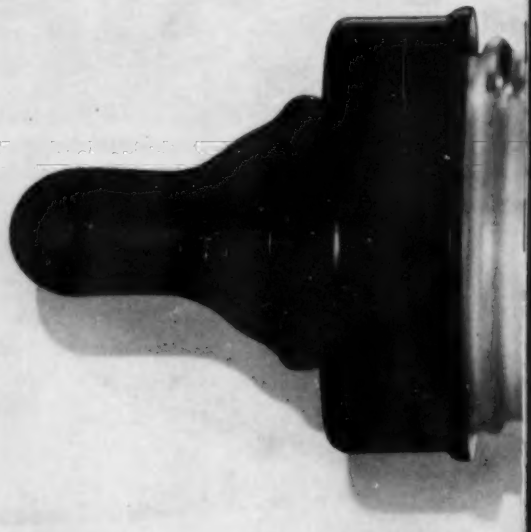

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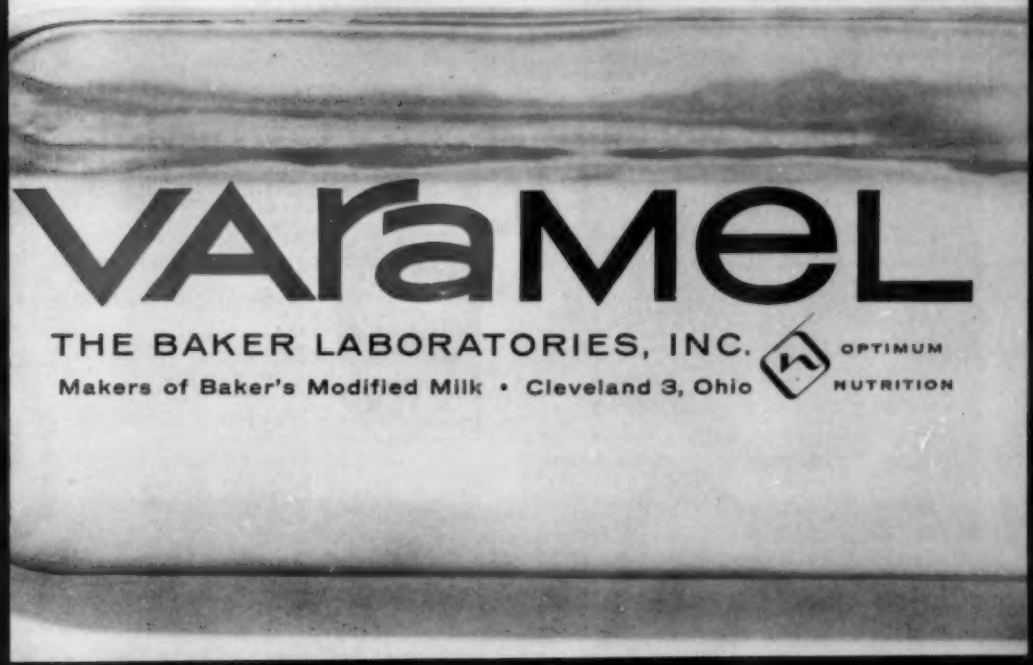

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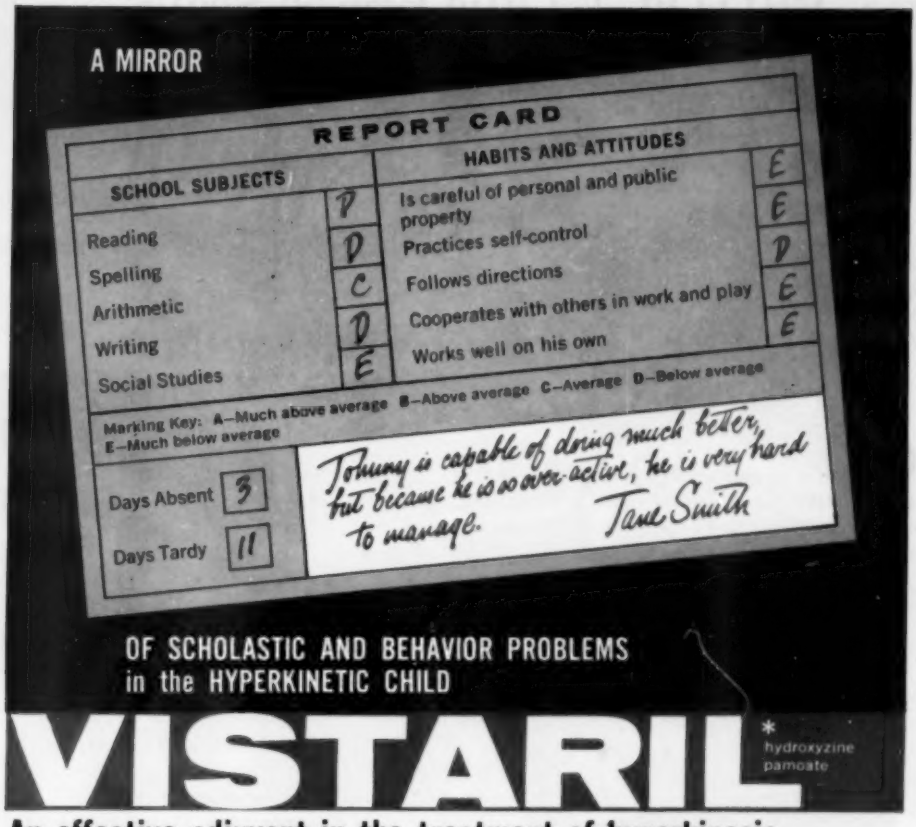

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REFERENCES: 1. Eisenberg, B. C.: Clinical Medicine *5*:897-904 (July) 1958. 2. Ayd, F. J., Jr.: Med. Arts and Sciences *2*:37, 1957. 3. Ayd, F. J., Jr.: New York State J. *57*:10 (May) 1957.

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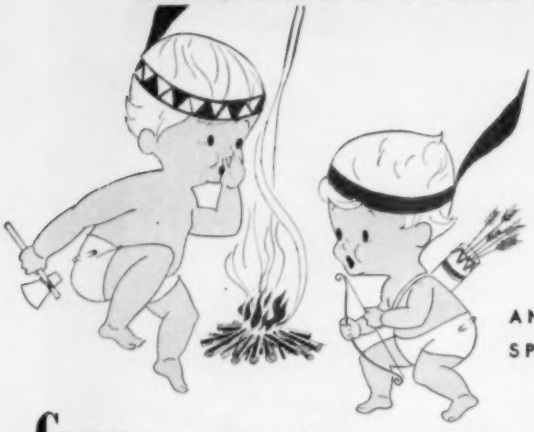

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Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

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NOW YOU can prescribe Meyenberg *Powdered* Goat Milk, and your patients can get it anywhere. Palatable and portable, Meyenberg *Powdered* is extra convenient for traveling... and costs less. Like Meyenberg *Evaporated*, Meyenberg *Powdered* Goat Milk is a medication of choice for cow's milk allergy. In some cases, however, it is preferable to prescribe Meyenberg *Powdered*—as in the case of older children. Because Meyenberg *Powdered* tastes just like dairy-fresh milk, the transition from cow's to goat's milk is a naturally simple one. *Powdered* or *Evaporated*, Meyenberg Goat Milk is nutritionally equal to cow's milk in protein, fat, carbohydrate and minerals. It provides a fine soft curd, readily digestible and free of crude fibers which may cause diarrhea. Always specify Meyenberg, your assurance of goat milk of the highest, most dependable quality. By Jackson-Mitchell Pharmaceuticals, Inc.—serving the medical profession for 25 years.

Formulae	MEYENBERG *Powdered* GOAT MILK		
	POWDER	WATER	CALORIES FL. OZ.
Introductory or Transitional	1 Tablespoon	1 Fl. Oz.	14
Standard Formula	1 Tablespoon	2 Fl. Oz.	20

Increase caloric value as desired by the addition of a carbohydrate.

FULL-SIZE TRIAL CAN AVAILABLE ON REQUEST

Powdered in 14 oz. cans, Evaporated in 14 fl. oz. cans.

JACKSON-MITCHELL *Pharmaceuticals, Inc.*

10401-A Virginia Avenue, Culver City, Calif.

they've heard the call for...

VI-DAYLIN®

now . . . VI-DAYLIN's more fun than ever in the new "Pressure Pak"

Just press the button—a golden stream of delicious VI-DAYLIN fills the spoon with *8 essential vitamins* flavored like lemon candy. New "Pressure-Pak" ends the problem of vitamin "won't takers" . . . Youngsters remind Mom when it's VI-DAYLIN time! No sticky cap, no mess, no waste, no refrigeration—can't break or spill.

The new 12-fl.oz. VI-DAYLIN "Pressure-Pak" is available at pharmacies everywhere. VI-DAYLIN is also supplied in 3-fl.oz., 8 -fl.oz. and pint bottles, at all pharmacies.

Abbott

®VI-DAYLIN—HOMOGENIZED MIXTURE OF VITAMINS A, D, B_1, B_2, B_6, B_{12}, C AND NICOTINAMIDE, ABBOTT

For CONSTIPATED BABIES and CHILDREN

Borcherdt's
MALT SOUP EXTRACT
(MALTSUPEX)

It's not a drug—it's a food supplement. It helps nature function normally by promoting favorable aciduric bacteria in the lower tract and creates and maintains soft natural stools.

Malt Soup Extract is a non-diastatic barley malt extract neutralized with potassium carbonate. It's harmless and, when necessary, can be given over a long period of time without any side effects. It causes no inflammation, no gas pains and restores a normal acid condition in the lower tract.

For babies two tablespoonfuls of Malt Soup Extract is added to the formula. For children two tablespoonfuls in milk (children love it) twice a day or use it on cereals or in fruit juice.

Some physicians prefer the liquid form. Many like the mild tasting, easily handled powder form. Both are available at drug stores coast to coast.

"8 oz. and 16 oz. bottles"

Borcherdt Company

217 North Wolcott Avenue, Chicago 12, Illinois

In Canada, Chemo Drug Co., Ltd., Toronto, Canada

We will be glad to send you clinical samples of powder and (or) liquid.

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Gentlemen: Please send me sample of Malt Soup Extract (☐ Powder ☐ Liquid) and literature.

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forestall the epileptic personality

Fear of seizures, parental attitudes and social rejection all threaten the epileptic child. Brain damage or the abnormal discharge itself may provoke psychic disorders.

Better control of seizures and better understanding by parents before a child starts school may prevent the development of an epileptic personality.

Highly effective: In most types of seizures, especially major motor seizures, **MEBARAL** is one of the safest anticonvulsants for children. This antiepileptic does not tend to lower learning capacity.

Unsurpassed safety: Mebaral is not likely to cause hyperactivity in young children. Toxic reactions or ill effects from it are rare.

MEBROIN,® combining Mebaral and diphenylhydantoin, is synergistic—and side effects are infrequent. Each relatively tasteless Mebroin tablet contains 90 mg. Mebaral and 60 mg. diphenylhydantoin. Mebroin brings maximal control of seizures with minimal toxicity.

Mebaral dosage: CHILDREN under 5 years, from ¼ to ½ grain three or four times daily; over 5 years from ½ to 1 grain three or four times daily. ADULTS from 6 to 9 grains daily.

Mebroin dosage: CHILDREN under 6 years, ½ tablet once or twice daily; over 6 years, 1 tablet two or three times daily. ADULTS, 1 or 2 tablets three times daily (average dosage).

For epilepsy at any age

MEBARAL®

Supplied: **MEBARAL** tasteless tablets of 200 mg. (3 grains), 100 mg. (1½ grains), 50 mg. (¾ grain), 32 mg. (½ grain). Bottles of 100.

MEBROIN virtually tasteless tablets. Bottles of 100.

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